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BRITISH MEDICAL JOURNAL

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RADIOTHERAPY IN ITS RELATION TO DERMATOLOGY*

BY

B. W. WINDEYER, F.R.C.S., D.M.R.E., F.F.R.

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The art and science of radiotherapy has been closely associated with dermatology ever since the first attempts at treatment with *x* rays were made within a few months of Röntgen's epoch-making discovery in November, 1895. It was the evidence of erythema of the skin, of dermatitis, and of necrotic ulceration, produced accidentally on the exposed hands and faces of enthusiastic workers or during prolonged demonstrations of the properties of the new-found rays, that gave the first indication of a biological reaction. Similarly the biological action of radium was discovered by the recognition of radium-produced dermatitis by Walkoff in 1900, and by the famous Becquerel burn in 1901 (Becquerel and Curie, 1901). Becquerel carried some radium in his waistcoat pocket and subsequently developed a painful ulcer on his chest wall.

Since those early days radiotherapy, by the use either of *x* rays or of the radiations from radioactive substances—in particular radium and radon and more recently some radioactive isotopes—has been used with benefit in a great number and variety of dermatological conditions. It has brought to dermatological practice an important method of treatment. Indeed, it is probably no exaggeration to say that for many dermatologists radiotherapy has been their most important single therapeutic agent. At the same time it must not be forgotten that radiotherapy has also brought to dermatology some new and difficult problems in the form of pathological conditions which are among the most distressing and tragic, and the most resistant to treatment which can occur.

In the content of this lecture it is not possible to describe all the dermatological conditions for which radiotherapy may be of value, but some discussion of the main groups and the underlying principles may be of interest.

In dermatological practice the effect which is required by radiotherapy is usually one which is limited to the skin and immediate subcutaneous tissues. It is therefore desirable to use a type of radiation which is soft and absorbed in the surface layers and does not penetrate deeply into the body. This is obtained by *x* rays of low voltage or by the beta rays from radium or other radioactive substances. There is no necessity, and it is undesirable, to use more penetrating radiation such as is useful for more deeply seated neoplasms, except in the case of some of the more infiltrating malignant skin tumours. What is commonly known as superficial *x*-ray therapy—that is, *x* rays generated at a tension of not more than 100 kV, and lightly filtered radium plates which allow a high proportion of the beta rays to emerge, have been the main methods of radiotherapy for skin diseases. In more recent years some beta-emitting isotope such as P^{32} or strontium^{90} has been used as a substitute for radium with certain advantages.

*Chadwick Trust Malcolm Morris Memorial Lecture given at St. Mary's Hospital, London, W.2, on December 3, 1953.

Action of Radiation in Dermatology

The use of radiotherapy in dermatology may be grouped into three main types of technique, each used for the treatment of distinct and different groups of disease with different dosage levels and with the object of producing different biological effects.

1. *Multiple Small Doses.*—A technique of multiple small doses is used for the treatment of inflammatory conditions and of many dermatoses. The size of each dose is often less and usually not more than 100 r—about a quarter of that which would produce a visible erythema—and the intervals between each dose are usually of about a week. It may be repeated four or five times in a course of treatment, but the repetitions must be strictly limited, as even with such small doses harmful sequelae will occur after prolonged or multiple courses of treatment. From the earliest days of *x*-ray therapy it became known that many inflammatory conditions, both acute and chronic, would regress and subside after such small doses of radiation, but although much work has been done and many facts have been accumulated the true nature of the action of radiation in effecting such results is not known. Theories have been advanced that the action is primarily on the blood vessels, causing dilatation and diapedesis, or that there is a destructive effect on the most sensitive cells, the lymphocytes, which are accumulated in the tissues irradiated, with the liberation of antibodies, or a destructive effect on developing fibroblasts. Whatever the exact mechanism may be there is some definite reaction produced, without any clinical erythema, which promotes the regression of these pathological processes. Similar techniques are used in the treatment of some haemangiomata in children and for keloids.

2. *Single Dose.*—A single-dose technique is used to produce temporary epilation in cases in which there is infection deep in the hair follicles. The dose given is one which will produce a mild erythema—that is, between 400 and 500 r with this quality of radiation—and it acts by causing damage to the sensitive cells lining the hair follicles. The hair falls out, leaving the follicles open and amenable to the application of fungicidal or bactericidal agents. The follicles regenerate after such dosage and the hair grows again.

3. In the treatment of malignant disease higher dosage is given, and it may be close to the maximum that the normal tissues will tolerate without irreparable damage. The whole basis of the radiotherapy of malignant tumours is that there is a difference between the radiosensitivity of many malignant growths and the normal tissues in which they grow. Such malignant lesions of the skin can be destroyed by doses which are not

sufficient to cause permanent irreparable damage to the skin and subcutaneous tissues. In most cases, however, the dose necessary will cause a marked inflammatory reaction, with subsequent dryness and permanent depilation. The biological reactions involved in the destruction of the tumour cells are of a complicated nature and involve alterations in the molecular structure of the intracellular protoplasm.

A single-dose technique may be used in the treatment of some superficial malignant tumours of limited extent and known radiosensitivity. This is convenient in such cases because it allows the treatment to be completed without numerous attendances. In larger and more infiltrating lesions a safer result with less damage to normal tissues is obtained by spreading the total dose out over a more prolonged period of time. This may be achieved by using a fractionated technique—that is, the total dose is spread over a period of some days or even weeks, and a daily treatment is given, delivering a predetermined fraction of the total on each occasion. When radium is used the same type of effect may be obtained by continuous irradiation with a small quantity of radium, spread over a period of days.

Inflammations and Dermatoses

Before the days of chemotherapy, *x* rays were used to treat pyogenic infections such as boils and carbuncles, with marked improvement as regards the relief of pain and induration. There is more rapid subsidence and the inflammatory process becomes more circumscribed. Erysipelas also was treated as a routine in some institutions. These are matters of historical interest now, but there is still a useful field for radiotherapy in the treatment of chronic paronychia, which may be resistant even to modern chemotherapy and which can be healed in the great majority of cases by doses of the order of 100 r or less, repeated at weekly intervals for four or five doses.

A variety of the more chronic types of dermatosis are treated in the same way. Patches of neurodermatitis respond well to the same order of dosage, and chronic eczema with lichenification, resistant to other methods of treatment, usually heals after three or four exposures.

X-ray treatment is of real value in many cases of chronic acne vulgaris with induration of the subcutaneous tissues. There is more doubt about its value in acne rosacea, but I believe that here too it has an important place in the skin manifestations, and certainly it is at present the most valuable method of treatment available to promote healing of the corneal infiltrations and to alleviate the distressing symptoms of pain and photophobia.

Lupus Vulgaris.—The value of *x*-ray therapy in lupus vulgaris has been the subject of considerable discussion. There is no doubt that many cases have healed after repeated doses of the order of 100 r at weekly intervals. In the course of years many patients have received gross overdosage, with the development of telangiectasis, excessive fibrosis, and subsequent carcinomatous degeneration, and there has been a tendency to consider that carcinoma developing on lupus is always the result of the *x*-ray treatment. There are, however, examples of lupus carcinoma when no *x* ray treatment has been given. The excessive scarring occurring in this disease is likely to give rise to carcinoma in the same way as carcinoma may arise in any other scar tissue, particularly the extensive scars from burns. Fortunately there seems to be good reason to expect that newer methods of treatment will be more efficacious and may make *x*-ray treatment unnecessary in this disease.

Psoriasis.—This was one of the first conditions to be treated by *x* rays. The lesions, whether on the skin or on the nails, respond well to small doses in most cases, but unfortunately they recur with almost unfailing regularity. The unfortunate patient then, not unnaturally, again seeks the remedy which has been so successful, and the process is repeated. There have been many instances in which excessive radiation has been given, perhaps by the accumulation of dose over a period of years by a succession of practitioners, with resultant sclerosis and telangiectasis and ultimately the development of malignant disease. It has been truly said, and it particularly applies to *x*-ray therapy, that volumes have been written not only about the cures for psoriasis but about the cures for the conditions produced by the cures for psoriasis. Of course, it is not always radiotherapy which causes cancer in psoriasis. There are cases of development of malignant disease in the absence of any irradiation, but I believe that psoriasis should be subjected to radiotherapy only in exceptional cases, when patches resistant to other forms of treatment are causing distressing symptoms, or for involvement of the nails.

Pruritus.—The same arguments apply to the treatment of pruritus. In many instances *x*-ray therapy will immediately cause relief of symptoms, but only too often the condition recurs, and then recourse is had again to the miracle treatment. The dangers of accumulation of dose are enhanced by the fact that the perineum and perianal regions are parts of the body naturally soft and moist, which are particularly sensitive to irradiation, and do not tolerate heavy dosage. It is difficult for the patient to realize the dangers of this apparently simple and rapid method of alleviating his discomfort, and he may go off to another unsuspecting practitioner when the original one refuses further treatment. There have been many real tragedies with extensive necrosis due to such treatment, and I consider that pruritus also should be treated by radiotherapy only in exceptional circumstances when there is a real dermatitis with lichenification, and after due warning to the patient.

Angiomata

The mixed capillary cavernous type of haemangioma, the so-called strawberry naevus, is often treated by irradiation, and the results of such treatment are almost universally satisfactory. These lesions are present at birth or appear shortly afterwards. They may grow with considerable rapidity during the first year of life, causing great alarm to the mother or they may show little progress, becoming actually larger but with an increase in size only proportional to the growth of the child. In some cases there may be no increase in size, and they may begin to regress and disappear completely within a few months without any treatment.

There is a tendency for all of them to regress within a few years, and it is doubtful if any but a small proportion would remain until adult life even without any treatment. There is no doubt that radiotherapy will make them disappear more quickly and more completely, and, apart from the general desirability of curing the deformity as quickly as possible, there are some cases in which treatment is urgently required. An angioma on the lip may interfere with sucking, or one on the eyelid may interfere with the function of the eye. Others may ulcerate and, if situated in or near the napkin area, may become infected.

Two or three suberythemal doses of superficial *x* rays or applications of beta-ray radium plates will ensure gradual regression, and in most cases this will continue until there is no sign of the lesion and the overlying skin will gradually attain practically normal texture. Complete regression with this form of treatment may take a year or two, but it is preferable to any attempt to cause rapid disappearance with larger doses, as they may cause atrophy and scarring of the skin. There have been instances where such larger dosage has been responsible for severe deformity by interference with the growth of a limb or the proper development of the bones of the face or orbit. More deeply seated cavernous haemangiomata may be effectively treated by the implantation of radon seeds with appropriately small dosage, which should be kept to 1,200 r as a maximum.

The use of radiotherapy in these lesions, if properly controlled with suitably small dosage, is in every way preferable

to treatment by carbon dioxide snow, which in most cases leaves an unsightly scar.

The central vein angioma, or spider naevus, is unsuitable for radiotherapy; and the capillary haemangioma, or port-wine stain, commonly occurring on the face and sometimes of considerable extent, also does not respond to this form of treatment. In order to obtain any improvement in the discoloration by the use of *x* rays or radium it is necessary to give such dosage that there will be some permanent damage to the texture of the skin. The cosmetic result is usually worse than if no treatment had been given except to cover it with make-up, and there is the real danger of severe scarring, necrosis, and even cancer formation in later years.

Thorium X has been used for the treatment of these stains, being contained in a solution which is painted on the surface of the lesion with the object of making use of its alpha rays with their limited power of penetration. Some dermatologists with experience of hundreds of cases so treated consider that a worthwhile improvement can be obtained, but I have not been able to convince myself of any appreciable effect.

Keloid

In the treatment of keloids and hypertrophic scars radiotherapy has an important part to play. When the keloidal scar is recent and still vascular and has not become organized into solid fibrous tissue, marked improvement can be obtained by the application of *x* rays or of radium two or three times at intervals of a month or six weeks. Each individual dose should be less than that which would cause an erythema, and care must be taken that the total dose is not excessive. There is subjective improvement with lessening of itching, tenderness, and pain, and the scar becomes paler, flatter, softer, and more pliable, so that there is an improvement in the amount of contracture that may be present. If the keloid is old, hard, and avascular it will not respond to radiotherapy. In such cases it should be removed surgically where possible, and the recent scar treated by radiotherapy to prevent recurrence of keloid. *X* rays are often used as a pre- or post-operative measure to prevent the development of thick and unsightly scars when surgical operations are undertaken in sites where a good cosmetic effect is essential.

Temporary Depilation

Ringworm of the scalp in children was first treated by Freund in 1897. Its success depends on complete temporary epilation of the affected area, which in fact means complete temporary epilation of the whole scalp. In the first years of radiotherapy there were many failures and accidents in the treatment of these children. Insufficient dosage at any point might mean that areas of infected hair remained on the scalp and the whole scalp became reinfected when the new hair grew again. There were cases of permanent epilation and of necrosis of the skin through overdosage, either in large patches or in strips between adjacent *x*-ray fields. There were also many successful cases. One of my colleagues had his scalp depilated for ringworm by Sir Malcolm Morris about 50 years ago. He has still an excellent head of hair.

In 1907 Kienböck described a method of giving irradiation to the scalp using five points of application. In 1909 Adamson, a British radiologist, described some modifications to this method, and ever since that time the Kienböck–Adamson technique has remained the most frequently used standard technique for irradiating the scalp in cases of ringworm. A four-field method is advocated by Shanks (1931) as a saving in time, but whichever is used the results, in careful hands, are now uniformly good. Ringworm of the scalp has been stamped out except for sporadic cases, and any real complications and sequelae from the treatment are of the greatest rarity.

Sometimes straight hair may grow back in curls after epilation and—much more serious—curly hair may turn straight. This fact has, however, its compensations. It is a well-known result among the coloured population of Washington, D.C., in the United States, and many mothers will apply irritants to their children's scalps so that they will simulate ringworm, be treated by epilation, and run a chance of getting straight hair.

Temporary epilation may also be necessary for the cure of resistant cases of sycosis barbae.

Malignant Disease

In the treatment of malignant disease of the skin radiotherapy has a role of great importance. In some cases it is the method of choice and should be used as the sole treatment. In some cases it is better to use a combination of radiotherapy and surgery and in others surgical excision alone should be employed.

The choice of method of treatment, the technique, and the dosage will be decided according to the clinical and histological features of each individual case. Radiotherapy may be given by *x* rays generated at high or low voltage, by surface application of radium, by radium needle implantation, by teleradium, or by some radioactive isotope used in any of these ways as a substitute for radium. A single dose, a continuous application, or a fractionated course of treatment may be the technique chosen.

Whatever it may be, it is essential for the curative treatment of malignant disease of the skin, as in cancer of other organs, to give the chosen form of radiotherapy as a single planned course of treatment. There is no place in the attempted cure of cancer for the multiple-small-dose technique. After possible initial regression the tumour becomes progressively more resistant and cannot then be cured even by more adequate dosage.

A second principle is that if failure has occurred after such a planned course of radiotherapy, a second attempt at treatment is unlikely to be successful and runs a risk of producing necrosis. Surgical ablation should then be carried out in the majority of cases, even though it may mean considerable disfigurement by sacrifice of tissue. In some cases of marginal recurrence outside the previously treated area a further course of radiotherapy may be successful, and may be undertaken without serious risk.

Rodent Ulcer

In small and superficial rodent ulcers there is little to choose between the curative results of radiotherapy and surgical excision. Radiotherapy may be chosen because of the better cosmetic effect in some situation, particularly in extensive lesions in which excision would entail a graft to cover the defect.

In superficial cicatrizing growths, which are often of considerable extent before the diagnosis is made, surgery may be impossible or may be practicable only at the expense of great deformity. Radiotherapy may be successful in such cases with only minimal resultant scarring. In some cases in which the eyelids or the conjunctiva is extensively involved the use of a combination of radiotherapy with surgery may be desirable. Preliminary irradiation may allow the surgical excision to be limited to a simple excision of the eyeball, instead of a wide exenteration of the orbit. Earlier, more limited lesions of the eyelids may be treated by irradiation with little scarring or deformity, and without damage to the eye if a contact shield is placed between the lids and the globe or if the beam of radiation can be directed away from the eye by displacing the eyelid during the treatment.

Squamous-cell Carcinoma

Squamous-cell carcinoma of the skin responds as well to radiotherapy as does basal-cell carcinoma. The percentage of cures is lower because the lesions are in general more extensive when they come for treatment, and because a proportion arise in scar tissue with poor blood supply. There are also a number of failures due to the development of glandular metastases. As a general rule involvement of bone or cartilage by direct extension of malignant disease means that the growth is less likely to be cured by irradiation and more likely to undergo necrosis. Careful technique with radiation of hard quality will, however, provide some

successes in these cases, and it is worth while attempting radiotherapy in the first place in cases such as those of the pinna of the ear, where subsequent surgical excision will not have been made more difficult or more extensive if recurrence or necrosis results.

Malignant tumours on the limbs are difficult to treat by irradiation owing to the likelihood of necrosis of underlying bone and tendons. Squamous-cell carcinoma of the lower limb which sometimes arises on the site of long-standing varicose ulceration is often extensive and infiltrating. It is usually best treated by amputation. In the upper limb, however, every effort should be made to conserve the functions of the hand, and success may be achieved even in lesions of great extent by surface application of radium on a moulded appliance over a period of not less than two or three weeks.

Epithelioma of Lip

Epithelioma of the lip may come within the province of the dermatologist. Here too the choice between radiotherapy and surgery must be carefully decided for each individual case. Radiotherapy may be chosen, particularly in growths extending along the lip margin, on account of the excellent cosmetic results. Surgery should be chosen in cases of recurrence after radiotherapy and in advanced cases with deep extension and involvement of bone. Surgery may be necessary for repair of the tissue defect where radiotherapy has successfully dealt with an ulcerating type of lesion.

In tropical and subtropical countries such as Australia or South Africa, where European populations have continuous exposure to hot sunlight, there is a much higher proportion of skin malignant disease than in this country. Radiotherapy is of enormous benefit, and is widely used for the treatment of multiple lesions, either hyperkeratoses which would progress to the development of cancer, or frankly cancerous lesions. There is a place for surgery too in the treatment of these patients with a multiplicity of lesions and the certainty that more will develop. The cosmetic results must be of minor importance, and anyway, in a dry and keratotic skin, the scars of multiple small incisions may not be more unsightly than those of multiple treatments by irradiation. Surgery is generally preferable to irradiation for malignant growths occurring on the trunk. The type of rodent ulcer is often the intradermal and superficial cicatrizing variety; when treated by irradiation they usually leave thin atrophic scars which are easily damaged if rubbed by clothing; the cosmetic effect is not important, and surgical excision is often quicker and easier for the patient than a fractionated course or prolonged continuous applications of radiotherapy.

Although successful results may be anticipated from adequate surgery or adequate radiotherapy of rodent ulcer and squamous cancer of the skin, even early growths which are superficial and apparently innocuous in appearance, if not adequately treated, will recur and they will infiltrate widely, causing destruction of underlying tissues and ultimately the death of the patient. There are also some few of them, with no obvious difference in their clinical appearance, which appear from the onset to be much less amenable to treatment and which, despite wide excision or apparently suitable radiotherapeutic technique, develop rapid and widespread recurrence.

Naevocarcinoma

Malignant melanoma, or naevocarcinoma, is one of the most rapidly developing and deadly forms of malignant disease. It is usually considered to be the supreme example of a radioresistant tumour for which surgery is the sole appropriate treatment. Recent observations have shown that some of these tumours are radiosensitive and that it is advisable to give wide and intense post-operative irradiation after surgical excision.

Reticuloses

The diffuse group of diseases affecting the reticulo-endothelial system, which includes mycosis fungoides, Hodgkin's disease, reticulum-cell sarcoma, lymphosarcoma, and the leukaemias, have dermatological manifestations, sometimes as the first presenting feature. Radiotherapy is of great value in the treatment of many of these eruptions as well as in the more deeply seated lesions in glands, viscera, and skeleton. They often are very radiosensitive and disappear rapidly with small dosage, but unfortunately they are not permanently arrested, and widespread recurrence almost invariably leads to a fatal termination.

Local Reactions

Often there is misconception about the type of local reaction which occurs after irradiation for the treatment of malignant disease. It may be necessary to give the maximum dose which the normal tissues will tolerate, and this may produce a moist desquamative reaction of the epidermis. It is less frequently seen nowadays, and is avoided whenever possible. It will heal rapidly in 10 to 14 days, leaving a dry, rather inelastic, and hairless skin with some pigmentation, and in individual cases there may be later development of telangiectases. This is the maximum therapeutic reaction which should be produced on the skin and should not be confused with an area of necrosis, the *x*-ray or radium burn, which is a deeper ulceration involving the dermis or deeper tissues.

Necrosis

Necrosis is the most serious complication of irradiation. It may occur as an immediate sequel to treatment with high dosage, in the form of early or acute necrosis. In such cases, following an early developing erythema which becomes a deep purplish colour, with some oedema of the affected part, the ulceration may extend rapidly, and is associated with severe pain. There is little tendency to heal, because of lack of blood supply, due to endarteritis of the vessels in the affected area. There is always marked secondary infection.

Acute necrosis occurs as the result of some error or accident in technique such as the use of the wrong filter, the overlapping of adjacent fields of irradiation, or some miscalculation or error in measurement of the time for delivering a prescribed dose. It may also occur as the result of lack of appreciation in the prescription of treatment of the dose which some particular area will tolerate. There are individual variations in resistance according to age and certain pathological states: infected tissues necrose more readily; certain parts of the body are more sensitive than others, particularly if bone is close underlying the skin or there is a deficiency of blood supply; the previous application of local irritants may increase sensitivity; and, in particular, previous irradiation renders the tissues more liable to necrosis.

Necrosis may occur when a deliberate risk has had to be taken and heavy dosage has had to be used as the only possible chance of curing the disease. Although necrotic ulceration is often thought to be a sign of inaccurate treatment it is inevitable that occasional instances should occur in the treatment of large numbers of cases of cancer. It may sometimes be the price that has to be paid for the cure of the disease. Necrosis should never occur, and the risk should not be run, when dealing with non-malignant conditions which can be treated by other means.

Necrotic ulceration may occur as a late phenomenon. An area which has been heavily irradiated has some deficiency of blood supply due to increased fibrosis and sclerosis of the blood vessels. Such a volume of tissue may not withstand the effects of trauma occurring at a later date and may break down with the development of ulceration similar to that of acute necrosis. For example, after the treatment of a malignant tumour of the skin excessive exposure to the sun or to frost-bite may precipitate necrosis even many years later. Heavily irradiated bone and cartilage are particularly liable to late necrosis, and the precipitating cause may be some accidental blow or even a local infection of minor degree. Necrosis of the jaw may occur following dental extraction even five and ten years after heavy irradiation for cancer of the tongue or mouth.

Carcinogenesis

Repeated small and suberythemal doses, each of which has no apparent clinical effect, may cause irreparable damage to the skin. The effects come on gradually and may not be seen until years after the irradiation. There is dryness of the skin due to destruction of sweat and sebaceous glands, permanent depilation, and loss of elasticity due to fibrosis of the dermis. There is also a diminution in subcutaneous tissue, and the skin develops a drawn, shiny parchment-like appearance, sometimes with the development of disfiguring telangiectasis. This stage will go on to the development of hyperkeratoses and papillomata; if occurring on the hands, cracks and fissures will occur around the nails, which become ridged and brittle. Eventually cancer will develop with induration of the base of the hyperkeratoses, or by extension of ulceration from the unhealed fissures. This is the type of reaction and sequence of events which occurred in the pioneer radiologists.

In 1904, nearly 20 years before the formation of the British *X*-ray and Radium Protection Committee, which led the way in setting up safe working conditions, Dr. Cecil Lyster, medical officer in charge of the electric department of the Middlesex Hospital, discussed the loss of sensation in his own fingers after repeated daily exposure, and stated: "It was not until after three months' constant exposure that I noticed my nails were becoming hard and dry with a tendency to split. The hair came off the back of my hands and I soon found the skin, where most exposed to the rays, became dry and scaly." He then used a pair of wash-leather gloves painted with white lead, and his hands improved. His account goes on to describe the ulceration which developed on the back of his fingers following the exposure of his ungloved hand for 20 minutes to *x* rays in May, 1903. His hands healed on that occasion, but unfortunately he developed cancer of the hands and died 17 years later. He was one of that gallant and unfortunately numerous band of *x*-ray martyrs who died as the result of changes induced by overexposure to radiation. There were other pioneers, and among them dermatologists, who suffered from the general effects of irradiation and succumbed from aplastic anaemia.

Discrimination in Use of Radiotherapy

These local and general reactions and sequelae, occurring sometimes 10 and 20 years after multiple treatments or frequent exposures, have drawn attention to the urgent necessity for discrimination in the choice of the condition for which radiotherapy should be used. I consider that as a principle it should not be used in any non-malignant condition for which a simpler and safer method of treatment will give equal chances of success.

Warts.—The place of radiotherapy in the treatment of warts is a question on which there is by no means general agreement. Many of them will disappear after adequate irradiation, but in most instances single warts of long standing, particularly those around and under the finger-nails, need a dose to the small area involved which is sufficient to produce a sharp erythema and perhaps desquamation. Warts on the plantar surface of the foot are a special problem; they can frequently be treated with complete success by a single dose of *x* rays or a single treatment by radium. This is particularly true of the infective plantar warts of children. The sole of the foot, in common with the palms of the hands and the perineum, is one of the most dangerous areas to irradiate. It is very liable to trauma, and necrosis may occur after heavy dosage. Sometimes warts have failed to disappear or have recurred and have been given a further dose, perhaps by another practitioner. In some cases callosities caused by faulty weight distribution have been treated as plantar warts and have inevitably recurred. Whatever the reasons, there have been numerous cases of severe and crippling necrosis following the treatment of warts, and I consider that, even though the majority can be treated easily and successfully without accident, it is wiser to withhold irradiation and to treat them all by safer methods such as surgical excision.

Cosmetic Treatments.—The use of radiotherapy for cosmetic reasons such as the removal of superfluous hair should be condemned, as it has been the cause of many real tragedies. Permanent depilation cannot be attained without running the risk of later skin changes, with much disfigurement and subsequent cancer formation. The permanent reduction in secretion of sweat can also be attained only with great risk, and hyperidrosis should be treated by irradiation only in exceptional cases. The risks inherent in the treatment of pruritus and psoriasis have already been discussed.

The type of skin cancer which occurs as the result of irradiation is usually squamous-cell epithelioma, but rodent ulcers have occurred and sarcoma has also been described.

Radiotherapist and Dermatologist

The advent of the radiotherapist has created some problems and some difficulties in deciding the exact place of the dermatologist and of the radiotherapist in the radiotherapy of dermatological conditions. These problems must be solved, and are being solved, by mutual good will and understanding, because both have some essential contribution to make. *X*-ray therapy is for many dermatologists such an important part of their work that they have installed their own *x*-ray therapy plants as a necessary adjunct to their dermatological practices. They have become accustomed to treating their patients with standardized techniques and have largely eliminated the dangers and accidents by using very small doses, which are all that is necessary for the majority of patients they treat. Naturally such experienced dermatologists consider that there is no necessity for the help of the radiotherapist and that they can be self-sufficient. On the other hand, there is a tendency for the radiotherapist to consider that all cases of malignant disease of the skin should undoubtedly be treated by him and should be in his sole care.

I do not think that these arrangements are satisfactory and in the best interests of the patient. Radiotherapy of all conditions is best conducted, and the best results will be obtained, if there is constant and close collaboration between the radiotherapist and his colleagues in other clinical specialties. In dermatological radiotherapy, collaboration between dermatologist and radiotherapist will bring the best results so far as the patient is concerned.

Apart from such technical questions as ensuring accuracy by proper calibration and measurement of dose, of ensuring homogeneity of irradiation over the field irradiated, and apart from questions of protection of patient and personnel and adequate maintenance of plant, the radiotherapist can bring his experience in the irradiation of other conditions. The use of this knowledge, added to the specialized clinical experience of the dermatologist, is most likely to ensure progress in this branch of therapy.

Such collaboration is also essential in the development of the proper use to be made of new methods of irradiation and new technical possibilities that are now available. The whole field of use of radioactive isotopes must be explored. Many of these are suitable for dermatological use, with greater convenience and safety than the established methods of irradiation, and can provide a variety of new techniques. There is also an urgent need for more knowledge of the biological effects produced by radiation in many of the conditions which are treated.

The period of 30 years since the death of Sir Malcolm Morris has seen many changes and much progress in radiotherapy in relation to dermatology. We are now in a period of intense activity and discovery, but there is still much to be done.

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TREATMENT OF ACUTE GASTRO-DUODENAL HAEMORRHAGE

WITH PARTICULAR REFERENCE TO QUANTITATIVE BLOOD REPLACEMENT

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During the year beginning in May, 1952, we treated patients with acute gastro-duodenal haemorrhage by a method incorporating the following principal features: (1) initial treatment by conservative measures; (2) early estimation, by means of a blood-volume determination, of the amount of blood lost; (3) quantitative replacement of the blood lost; (4) repetition of the blood-volume estimation to determine if haemorrhage has ceased or has recommenced; (5) early surgical intervention in cases of haemorrhage continuing or recurring in spite of conservative treatment.

We have been impressed with the increased saving in life since the inception of this therapeutic regime, and, while our own trial continues, publication of clinical detailed results obtained to date seems to be warranted.

The treatment of acute gastro-duodenal haemorrhage is still controversial. Agreement is lacking on such points as the diet to be given, the quantity of blood to be administered and the rate of transfusion, and the indications for emergency surgical operations.

It is difficult to compare the results furnished by various means of treatment, because of fundamental differences in the material reported on by the authors. Such differences are particularly noteworthy in the age and social grouping of patients studied and in the average severity of the haemorrhage: whereas some authors include all cases of bleeding in their series, others select only those of "severe" or "massive" haemorrhage; and the criteria by which the assessment of the severity is made vary widely.

One further source of differences among the various published accounts is worthy of emphasis. While some report "personal" series treated by outstanding specialists in this field, others summarize work carried out at general hospitals by heterogeneous medical groups without special facilities for selection or segregation of patients. The treatment described in this paper was carried out by a staff of general physicians and surgeons of varying experience, and the results represent the work of some 15 individuals. We believe that a similar scheme could readily be organized at any well-equipped general hospital.

Definition.—The term "gastro-duodenal haemorrhage" as used here denotes bleeding arising from intrinsic lesions of the stomach or duodenum. It excludes bleeding from oesophageal varices. "Acute" means bleeding at or shortly before the first examination.

Principles of Treatment

At Christchurch Hospital, at the present time, all patients stated to be suffering from acute gastro-duodenal bleeding are initially admitted to a surgical ward and seen by the surgeon dealing with acute cases. A physician is always on call, particularly when a patient's suitability for operation is being considered. Emphasis is laid on conservative treatment in the early stages, and adequate blood transfusion is regarded as its most important part. Only when this is seen to have failed to arrest the bleeding, or in cases of recurrent haemorrhage, is surgical intervention considered. We believe that non-arrest of bleeding should be diagnosed within 48 hours of admission and that the decision to operate should be made during that period.

Blood Transfusion

The purpose of blood transfusion is twofold: to relieve shock and other symptoms resulting directly from loss of blood and to raise the patient's haemoglobin concentration to a level permitting adequate oxygenation of vital organs, such as the heart, liver, kidneys, and brain, and giving the best possible chance to the surgeon if he should be forced to intervene. It is widely recognized that emergency surgery carried out on anaemic patients is beset with a high and possibly prohibitive mortality, especially if the anaemia is of any length of standing. Prevention and rectification of anaemia seem to us to be the most important single aim in the initial treatment of acute gastro-duodenal haemorrhage, and we believe that, whenever there is evidence that blood has been lost, the extent of the loss should be ascertained and the deficit made good as rapidly as possible.

It was pointed out by Bennett *et al.* (1938) that in the early stages of most cases of acute haemorrhage an examination of the peripheral blood alone can give no valid information about the amount of blood lost, because cells and plasma are lost in equal proportion, and anaemia cannot be diagnosed until the plasma volume is restored by means of haemodilution. This classical paper has not received the attention it merits, and the severity of haemorrhage is still estimated by most investigators in terms of the haemoglobin level or red-cell count. Thus Crohn (1953) defines "massive" haemorrhage as that which is accompanied by shock and a lowering of the red-cell count to 3,000,000 or less per c.mm. or the haemoglobin level to 7.5 g. or less per 100 ml. In our series, following the advice of Bennett *et al.*, we have estimated the blood loss by means of a determination of the blood volume, and have used the figures so obtained for prescribing the quantity of blood to be transfused, the aim being restoration of the total red-cell mass to the figure calculated to be normal for each patient.

Other Therapeutic Measures

The *diet* is regulated according to individual requirements. Although we do not regard initial starvation as desirable we have found that many patients suffering from considerable degrees of gastro-duodenal haemorrhage tolerate early feeding badly and prefer to take only sips of fluid, at least during the first 12 hours. We give a semi-liquid gastric diet as soon as patients can take it comfortably. Nothing seems to be gained by forcing patients to eat or drink in the intervals between haematemeses.

Colloidal antacids have generally been given from an early stage, especially where pain persisted.

Sedation seems an important aspect of treatment, and includes not only drugs (we prefer not to use morphine in patients who are vomiting) but also liberal reassurance by the attending practitioner. When apprehensive patients are suddenly translated to an unfamiliar environment and then subjected to a series of investigations, which though necessary are puzzling to them, brief explanations and friendly reassurance can do much to ensure the success of treatment.

Surgery

During recent years it has become evident that in certain cases haemorrhage from the stomach or duodenum will not

subside under conservative treatment, however long continued, and that surgical removal or obliteration of the bleeding lesion is necessary. Two courses are open to the surgeon: either to operate on all except mild cases of haemorrhage (Finsterer, 1939; Stewart *et al.*, 1950) or to attempt to select those patients in whom conservative treatment is likely to be unsuccessful. We have adopted the second course, subjecting to emergency surgical treatment two classes of patients: (1) Those who in spite of conservative treatment, including adequate blood transfusion, showed evidence of bleeding at the end of 48 hours' observation in hospital—the operation, preceded by appropriate measures of resuscitation, being performed as soon as such a diagnosis had been made. (2) Those who, following cessation of the original haemorrhage, showed evidence of recurrent bleeding while still in hospital.

The operation of choice was partial gastrectomy, but in one case this was not thought to be feasible because of the patient's poor condition, and a local repair was done.

Technique of Blood-volume Estimation

We have used exclusively Gregersen's (1944) Evans blue method for determining the plasma volume (V_P), and have found it convenient and accurate enough for emergency use. Only slight modifications in Gregersen's technique have been necessary in our series. Thus the chromogenicity of the dye used by us was so high that the recommended injection of 25 mg. could sometimes not be repeated within 48 hours without producing a rather alarming slaty-grey staining of the patient's skin and mucosae. For this reason we injected the full dose only in exceptionally large patients, while in those of small and medium stature we gave 15 to 20 mg. on each occasion. Calibration standards were prepared from dye diluted solely with plasma. We have now performed well over 300 blood-volume estimations with this dye and have noted no sign of toxicity in any patient.

In the calculation of the total blood volume (V_B) and the total red-cell mass (V_C) we have made use of the venous haematocrit reading, multiplying it by a factor of 0.96 to correct for trapped plasma. We realize that an error was thereby introduced, as the total body haematocrit reading is lower than that of the venous haematocrit, and that the correction factor 0.86 would have given a more accurate result (Mollison, 1951). For the purpose of computing the amount of blood to be transfused the calculated V_C was compared with the "ideal" V_C. The latter was obtained by multiplying the patient's "ideal" weight (from Life Tables, using the patient's height and age) by the figure 36 ml. per kg. body weight. The work of Reeve and Veall (1949) has indicated that 30 ml. of red cells per kg. is a better estimate of the "ideal" V_C. The second error thus introduced into our calculations acted in the opposite direction to the first and partly cancelled it. We have calculated that by using the older figures mentioned we overestimated blood losses by from ½ to 1½ pints (284 to 850 ml.) per patient, according to the severity of the haemorrhage. This error does not appear to invalidate the results of our investigations, which were carried out under emergency conditions and not intended to supply fundamental data. When successive blood-volume estimations were compared for the purpose of establishing the presence or absence of continued bleeding the errors mentioned above did not influence our calculations, as we were comparing two sets of figures both obtained with the use of the same factors.

Using the Evans blue technique in non-bleeding patients, we have found successive estimations of the V_P to agree to within 5%, as claimed by Gregersen. Great care in injecting the dye, in removing samples of blood, and in estimating dye concentrations (using a Coleman spectrophotometer at a wavelength of 625 mμ) was, however, necessary to obtain such results, and all these operations were carried out by experienced senior laboratory staff. As few of our patients were able to take much food at the time of our examinations we have had little trouble with turbid plasma samples. Difficulties occasionally arose in estimating the height and weight of gravely ill patients, and in some cases we found it inadvisable to use the "ideal" weight for calculating the "ideal" V_C owing either to the presence of gross obesity or to malnutrition. In these cases we used a figure lying between the actual and the "ideal" weight.

Technique of Transfusion

All patients were transfused by means of the continuous-drip method with either stored whole blood or packed red cells. The normal rate of transfusion was one pint (570 ml.) in four hours. This rate was generally exceeded for the first one or two bottles of blood in the more severe cases of haemorrhage; when active bleeding was obviously proceeding, and particularly when patients were being prepared for emergency operations, blood was often given at very rapid rates and sometimes simultaneously into two veins.

As already stated, our aim was to restore the total V_C to the "ideal" by means of transfusion. For this purpose we assumed a pint bottle of stored blood to contain 200 to 220 ml. of red cells. If, therefore, we found a deficit of 1,000 ml. in the V_C we would give four to five bottles of whole blood. Packed red cells were often given when a patient's V_P was found to be large compared with his V_C, and especially when heart failure was present. In a few cases incipient congestive heart failure with a large V_P appeared to make it advisable to leave the patients with a blood volume of only about 80% of the calculated normal.

Material

During the year since the adoption of this therapeutic regime we treated 88 cases of acute gastro-duodenal haemorrhage: males, 69 (78%); female, 19 (22%). Five of these were admitted twice during the year, so that the series comprises 93 separate admissions. In addition several other patients were on admission thought to be suffering from haematemesis or melaena, but were on investigation found to have lost only insignificant amounts of blood. We decided to exclude these from our series. Table I shows the age

TABLE I

Age Incidence among 93 admissions (88 patients):

0–29 years	2	60–69 years	24
30–39 ,,	4	70–79 ,,	31
40–49 ,,	13	80–89 ,,	4
50–59 ,,	15		

Average Age, 62·6 years:

Over 50 years	74 (78·5%)
,, 60 ,,	59 (63·5%)
,, 70 ,,	35 (37·7%)

incidence among our patients. It will be seen that the great majority were middle-aged or elderly. This is in contrast to many other published accounts in which acute gastro-duodenal haemorrhage appeared to be most common among the younger age groups. As has been found by others, men were more commonly affected than women, although their preponderance was unusually heavy in our material.

Diagnosis

The diagnoses made in our 88 patients were as follows: gastric ulcer, 29 (male 25, female 4); duodenal ulcer, 26 (male 19, female 7); stomal ulcer, 2; probably peptic ulcer, 4; ulcer not visualized, 20; hiatus hernia, 2; gastritis, 3; carcinoma of stomach, 2. A definite diagnosis is indicated only when it was proved radiographically, at gastroscopy, operation, or necropsy. The group of four patients classed as cases of "probable peptic ulcer" had ulcers proved on previous occasions, but no ulcer was found during the current admission. Patients listed under the heading "ulcer not visualized" had strong histories pointing to peptic ulceration, but no actual lesion could be demonstrated. The policy at our hospital has so far been to wait at least one week after presumptive cessation of the haemorrhage before undertaking radiological or gastroscopic studies. Inevitably some of the more acute ulcers must have healed in the intervening period and their visualization thus became

impossible. A few emergency radiological examinations were carried out immediately before operation. In two cases no lesions were found at operation, but after gastrectomy bleeding ceased. It is probable that in at least one of these a high gastric ulcer was left behind.

Results

Table II shows the reduction in the red-cell mass found in those patients who had not been transfused at the time when their blood volume was first estimated, and in another six

TABLE II.—*Reduction in Red-cell Mass (% of Normal)*

	0–19%	20–49%	50+%
Patients not yet transfused	4	24	35
,, transfused but suffering from recurrent haemorrhages	—	1	5
Total	4 (6%)	25 (36%)	40 (58%)

who had recurrent haemorrhages after their first transfusion. Following the suggestion of Bennett *et al.*, we have arranged these individuals into three groups according to the magnitude of the blood loss. The "mild" group, with a reduction of up to 19% in their V_C, comprised 6% of the total; the "moderate" group, with a reduction of 20 to 49% in the V_C, 36%; and the "severe" group 58%. The last-named group lost more than 50% of their V_C. If a reduction in the V_C of 40% or more had been taken as implying "severe" or "massive" haemorrhage, as was done by Stewart *et al.* (1950), 78% of our patients would have fallen into this class.

The quantity of blood given is indicated in Table III. It will be seen that only about 25% had small transfusions of up to 4 pints (2.3 litres), while over 20% had more than

TABLE III.—*Quantity of Blood Given (93 Admissions)*

0–2 pints (0–1·1 l.)	7	9–10 pints (5·1–5·7 l.)	5
3–4 ,, (1·7–2·3 l.)	16	11–15 ,, (6·3–8·5 l.)	13
5–6 ,, (2·8–3·4 l.)	22	16–20 ,, (9·0–11·4 l.)	4
7–8 ,, (4·0–4·5 l.)	23	Over 20 ,, (over 11·4 l.)	3

Average, 7·9 pints (4.49 l.)

10 pints (5.7 litres) each. The average, 7.9 pints (4.49 litres) per patient, is among the highest reported. It equals that used by Stewart *et al.* in their patients undergoing emergency surgical treatment.

In the great majority of our patients the initial treatment was solely by medical means (Table IV). Only 14% had

TABLE IV.—*Initial Treatment*

Medical	80 (86%)
Surgical (Gastrectomy, 12; Closure of ulcer, 1)	13 (14%)
Diagnosis in surgical cases:	
Gastric ulcer	6
Duodenal ulcer	3
Gastritis	2
No lesion discovered	2

emergency surgical operations. "Interval" gastrectomies were carried out in another 17 patients (18%) after cessation of the bleeding. One-third of all individuals therefore underwent operations either during or after the haemorrhage.

Among 93 admissions there were seven deaths, making a mortality rate of 7.5% (Table V). One further patient died from a cerebral haemorrhage ten days after cessation of

TABLE V.—*Mortality*

	Survivals	Deaths	Mortality
Medical treatment	75	5	6·6%
Surgical treatment	11	2	15·4%
Total	86	7	7·5%

a bout of melaena. As he had advanced arterial disease with hypertension and a history of a previous cerebral accident, we believe that his death was coincidental with the condition for which he was admitted and that he should not be included in our list of deaths from the effect of acute gastro-duodenal haemorrhage. With medical treatment alone the mortality was 6.6%, while among the 13 patients treated surgically two died (15.4%). If the patient treated by cauterization of the bleeding vessel who succumbed to a recurrent haemorrhage is omitted from the "surgical" group, the mortality among the 12 patients treated by emergency partial gastrectomy was 8.3%.

Particulars of the fatal cases are given in Table VI. Their average age was 65.4 years and did not differ significantly from that for the whole series. Several of them had serious

TABLE VI.—*Particulars of Fatal Cases*

Age	Sex	Diagnosis	Operation	Complications	Cause of Death	Death avoidable
71	M	Gastric ulcer (acute)	Closure of ulcer	Severe chronic asthma with heart failure	Recurrent haemorrhage	?
59	M	Gastric ulcer	—	Hypertension and obesity	Uncontrolled haemorrhage	+
45	F	,,	—	Abdominal and generalized tuberculosis	,,	—
84	M	Duodenal ulcer	—	Senility. ? Excessive blood transfusion	Heart failure	?
70	F	Gastric ulcer	—		Uncontrolled haemorrhage	+
67	M	Duodenal ulcer	Partial gastrectomy		Inhalation of vomit at operation for repair of ruptured gastrectomy wound	+
62	M	Gastric ulcer	—	Perforation of gastric ulcer	Shock and haemorrhage	?

complicating diseases and were obviously poor surgical risks. Nevertheless we feel that at least three might have been saved by more rapid transfusion followed by operation. Only one patient, a 45-year-old Maori woman with gross abdominal and general tuberculosis in addition to an enormous gastric ulcer, appears in retrospect to have been doomed, whatever the treatment.

The following three cases are quoted to illustrate some of the details of our methods of diagnosing and treating acute gastro-duodenal haemorrhage.

Case 77

A man aged 37 was admitted eight hours after having vomited a small quantity of brownish fluid; he felt faint. He had had a similar episode nine years previously, when a diagnosis of duodenal ulcer was made. On examination he was a rather pale young man but not in distress. His pulse rate was 100; blood pressure 170/110; haemoglobin, 14 g. per 100 ml. Within two hours of admission the blood volume was found to be: V_B 62% of normal, V_P 68%, V_C 55%, indicating a deficit of 6 to 7 pints (3.4 to 4 litres) of blood (see Fig. 1). As this was an early case in the series

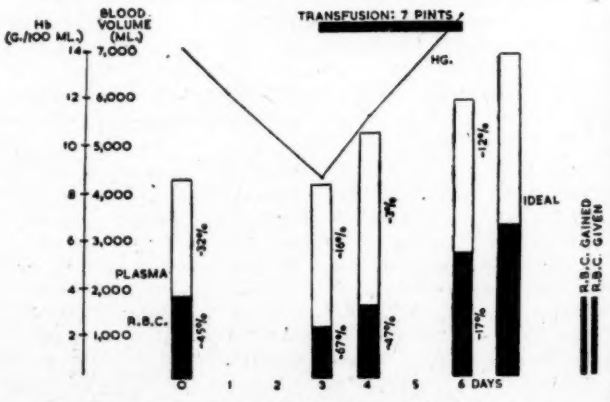

FIG. 1.—Case 77; blood-volume estimations.

and the patient's condition seemed to be good, no action was taken at this stage, but the blood volume estimation was repeated three days later. During this time there had been no further vomiting, the bowels had not moved, and the patient felt moderately well. The haemoglobin had fallen to 8.5 g. per 100 ml. The second estimation showed V_B 60%, V_P 84%, and V_C 33%, suggesting a further loss of about 3 pints (1.7 litres) of blood, with partial restoration of the plasma volume. Transfusion was now started, a total of 7 pints (4 litres) of whole blood being given. Further estimations demonstrated that the gain in V_C equalled the quantity of red cells administered, and this was evidence that bleeding had ceased. Large stools containing altered blood were passed from the fifth day onward. Radiography later demonstrated considerable deformity of the duodenal cap. The patient also suffered from advanced essential hypertension.

Comment.—This case history demonstrates an instance of an almost silent haemorrhage from a duodenal ulcer. On admission the patient's condition was good and his haemoglobin level normal. Yet a blood-volume estimation revealed a very considerable red-cell deficit. It was later possible to show by the same means first a further haemorrhage and then its arrest, all before there had been any overt signs of bleeding. When melaena occurred it was proved not to indicate renewed bleeding.

Case 53

A man aged 67 was admitted four days after a fainting spell. There was no vomiting or melaena. He had had abdominal pain for two and a half years. During a recent cholecystectomy for the relief of this pain a mass was discovered on the posterior surface of the stomach and interpreted as a probable penetrating gastric ulcer. Soon after admission the patient passed a large melaena and collapsed. His blood pressure was 90/55; haemoglobin, 8 g. per 100 ml. Blood-volume estimation showed V_B 73% of normal, V_P 98%, V_C 42% (Fig. 2), indicating a total deficit of about 6 pints (3.4 litres) of blood. A transfusion was started, with improvement of his condition. A second blood-volume estimation 36 hours later showed V_B 97%, V_P 105%, V_C 80%, and no significant difference between the quantity of blood administered and retained. It was concluded that bleeding had then been arrested.

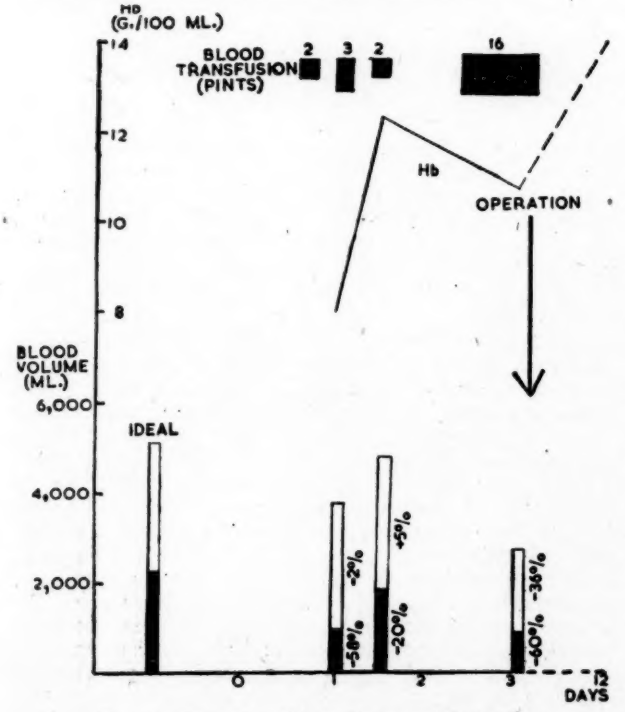

FIG. 2.—Case 53; blood-volume estimations.

Twenty-four hours later the patient collapsed again and passed another stool containing much blood. Blood-volume estimation showed V_B 53%, V_P 64%, V_C 40%. Emergency operation was decided upon, and was carried out after the transfusion of 6 pints (3.4 litres) of blood in three hours. At operation the splenic artery was found eroded by a large gastric ulcer adherent to the pancreas. The artery was tied and subtotal gastrectomy with splenectomy was performed, the ulcer being oversewn. The patient recovered. A total of 23 pints (13 litres) of blood had been given.

Comment.—The interest of this case lies in the use of blood-volume estimations to show a temporary arrest of bleeding and also the extent of both the primary and the recurrent haemorrhage. The blood volume was initially almost completely replaced by means of transfusion, and we believe that this enabled the patient to withstand the effects of the grave recurrent haemorrhage and to be prepared for a major emergency operation, which was successful.

Case 39

A man aged 47 was admitted with a history of severe upper abdominal pain for the past four days, black stools for two days, and vomiting of bright blood shortly before

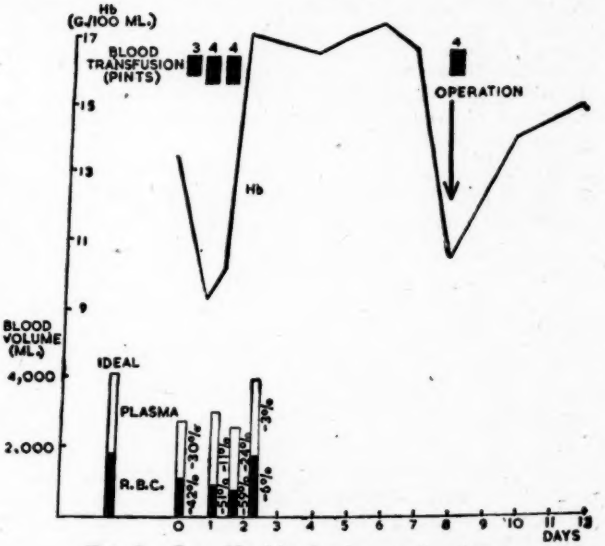

FIG. 3.—Case 39; blood-volume estimations.

arrival in the ward. He had had indigestion for seven to eight years, and asthma for the same period. He was shocked, sweating, and orthopnoeic. His blood pressure was 78/50. His chest was emphysematous, and there were marked movements of the accessory respiratory muscles. Blood-volume estimation showed V_B 65% of normal, V_P 70%, V_C 58% (Fig. 3), with an estimated deficit of 3½ pints (2 litres) of blood. Overnight he was given 3 pints (1.7 litres) of blood with clinical improvement, but a second blood-volume estimation, which showed V_B 71%, V_P 89%, V_C 49%, suggested a further loss of about 4 pints (2.3 litres) of blood when the transfused blood was taken into account. Further transfusions were given, his condition remaining poor mainly because of severe asthma. The next day there was great improvement and the blood volume was substantially normal. It was concluded that bleeding had now ceased, and the patient continued to make progress. Daily haemoglobin estimations showed a steady level, but six days later it was noted that it had dropped by 6 g. per 100 ml. in 24 hours. The patient looked a little pale, but his clinical condition was excellent and there had been no overt bleeding. An emergency operation was now carried out following the rapid transfusion of 4 pints (2.3 litres) of blood. Two large gastric ulcers were discovered—one with a large actively bleeding artery in its floor. After a partial gastrectomy the patient recovered. A total of 15 pints (8.5 litres) of blood had been given.

Comment.—This patient, in addition to bleeding from gastric ulcers, was suffering from severe chronic asthma and emphysema, and his condition during the first two days was extremely poor and probably precluded surgery. By means of repeated blood-volume estimations it was possible to show arrest of the bleeding within 48 hours of admission. Adequate blood transfusion restored his blood volume to normal and so improved his clinical condition that gastrectomy could be safely undertaken a week later, when haemorrhage recurred.

Discussion

The scheme of treatment here described was introduced in an effort to improve our results, which we had judged to be unsatisfactory. There were two fundamental considerations which led us to its adoption :

(1) It appeared improbable that we should be able to gauge the extent and duration of bleeding by the means usually employed—namely, an analysis of the clinical features plus estimations of the haemoglobin content of the peripheral blood. We therefore tested the possibility of using blood-volume estimations.

(2) We regarded prompt replacement of the lost blood as the single most important measure in conservative treatment, and also as an indispensable preliminary to surgery. The usually quoted indications for transfusion did not appear precise enough; it seemed logical, once the extent of the blood loss had been determined, to replace it as completely as possible and thereby to give the patient an optimum chance of healing his ulcer and of withstanding further bleeding, should that occur.

Below we examine the validity of these two considerations in the light of our findings.

The results of the initial blood-volume estimations are shown in Fig. 4, where the Vc on the abscissa is charted against the initial haemoglobin concentration. Only those

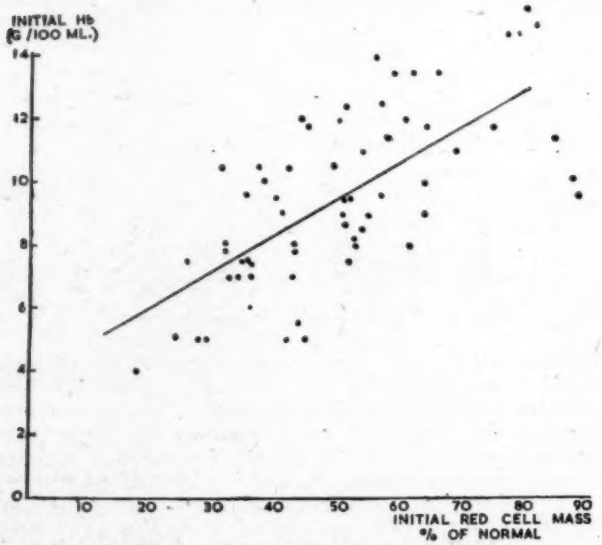

FIG. 4.—Results of initial blood-volume estimations.

patients who had not been previously transfused are included. It will be seen that, as might be expected, there is a general positive correlation between the two levels; however, more significantly, there are numerous striking exceptions in which a high initial haemoglobin concentration is paired with a low Vc. The findings reproduced in Fig. 4 are summarized in Table VII. In column 4 of this we also give the amount of blood calculated to be necessary to raise the initial Vc to normal in all patients in the various groups of severity. For instance, among the seven patients with initial haemoglobin concentrations of 4 to 5.9 g. per 100 ml. the initial Vc was 23 to 44% of normal, and 7 to 11 bottles of blood would have been required in individual cases to bring the Vc to the calculated normal. Again there is a general correlation between the initial haemoglobin level and the *average* amount of blood required. But the departures from the average become more and more marked as the initial haemoglobin level rises. Thus among the 10 patients with levels exceeding 12 g. per 100 ml. the initial Vc varied from 43 to 81% of normal and the quantity of blood required to raise it to normal from 2.5 to 9.5 bottles.

TABLE VII.—*Correlation Between Initial Haemoglobin Level and Red-cell Mass (63 Admissions Previously Untreated)*

Initial Hb (g. per 100 ml.)	No. of Patients in each Group	Initial red-cell Mass (% of Normal)	No. of Bottles of Blood required to raise Red-cell Mass to 100%
2–4	1	17	
4–5·9	7	23–44	7–11
6–7·9	15	25–61	6–10
8–9·9	16	31–88	2–8
10–11·9	14	30–87	1·5–9
12+	10	43–81	2·5–9·5

We believe that these figures show vividly the difficulty of gauging the severity of bleeding from haemoglobin estimations. Whereas the lower levels generally give a good indication, the higher ones often do not; the reason is that the high haemoglobin levels tend to be found soon after an acute haemorrhage and before there has been time for haemodilution to occur. At that time there is no possibility of knowing the eventual haemoglobin level or how soon it will be reached. Consequently it is impossible to estimate the quantity of blood which it will be necessary to give.

The problem of establishing continuance or cessation of bleeding in some cases is too well known to need elaboration; yet on its solution depends the treatment to be given. By means of repeated blood-volume estimations we have often been able to come to a definite decision, and to distinguish between the two causes of a falling haemoglobin level—haemodilution and continued bleeding. In this connexion the limits of accuracy of our method must be taken into account: before it was possible to diagnose further loss of blood the difference in successive estimations must exceed the experimental error. We have taken deficits in excess of 200 ml. of *red cells* as positive evidence of bleeding. There have been only a few cases in which interpretation of the findings was doubtful.

The indications and purpose of blood transfusion in acute gastro-duodenal haemorrhage vary with the views of different authors writing on the subject: "the presence of sweating or restlessness; anaemic pallor, as shown in the palms of the hands and in the conjunctivae; or a haemoglobin level of 60% or under are our indications for immediate transfusion" (Ogilvie *et al.*, 1952); "the object [of transfusion] was to make the patient fit enough to stand a possible recurrence of haemorrhage or an emergency operation" (Ferguson and Wyman, 1951); "give [blood] at an estimated hydrated 3,000,000 [R.B.C. per c.mm.] and stop at 4,000,000" (Rossett and Stephenson, 1952); "transfusion in every case" (Alsobrook *et al.*, 1952); "early transfusion with the aim of raising the red-cell count to 3,500,000 per c.mm." (Gott *et al.*, 1952). These few excerpts from recent papers show the wide divergence of opinion which still exists. In most of the older publications transfusion was the exception rather than the rule.

We regard transfusions as being of prophylactic as well as of immediate therapeutic value. When symptoms and signs of shock are present transfusion is obviously a matter of urgency; but people may lose large amounts of blood without accompanying shock, and the fallacy of judging the size of the loss from haemoglobin estimations has already been pointed out. Such patients may readily develop severe shock if further bleeding takes place, and their resuscitation at that stage may be a problem of the greatest difficulty, while emergency surgery may then be impossible. Moreover, a mild or moderate haemorrhage may progress to a severe one. Further, it is well recognized that the presence of anaemia impairs the action of organs like the heart, liver, and kidneys, and probably also the chances of healing at the ulcer site. It is likely that patients over 50 are progressively less tolerant of anaemia, and that this accounts for the rising mortality in the older age groups. Nearly 80% of

our patients were over 50. These arguments have persuaded us to transfuse every case of acute gastro-duodenal haemorrhage and to attempt to replace completely all the red cells which have been lost.

Many observers have in the past stated their fear lest transfusion may cause renewed bleeding once it has been arrested. Like other recent authors, we have found no evidence of this happening in our patients. It is probably of some importance to give the blood slowly so as to increase the blood volume and raise the blood pressure gradually, but this should not preclude rapid administration where there are signs of shock or the patient has to be prepared for emergency surgery. It is likely that prolonged hypotension contributes significantly to the fatal outcome in some cases, and slow transfusion may not be adequate to raise a dangerously low blood pressure to a safe level.

The transfusions given by us were generally large and often massive. The danger of overtransfusion has been widely discussed, and in our patients we have watched carefully for any signs which might have indicated it. It is gratifying that with one exception these have been completely absent. The exception was a man of 84 who died several days after arrest of bleeding from a chronic duodenal ulcer and after transfusion of 7 pints (4 litres) of whole blood. At necropsy moderate pulmonary oedema was present; possibly this was partly caused by the transfusion and might have been avoided if packed red cells had been given instead of whole blood. This patient was, however, extremely senile, and death did not occur during or soon after transfusion; nor were any signs of respiratory distress noted at any stage. For these reasons the significance of the transfusion causing death was doubtful. This fatality occurred early in our series, and since then we have often given packed red cells instead of whole blood, especially when the history of bleeding extended over several days and when the plasma volume was in the vicinity of normal. It should also be mentioned that severe haemorrhage in elderly patients sometimes causes signs of acute coronary insufficiency with or without congestive heart failure, and that in this series there were several instances—at least three with actual myocardial infarction. All of these were greatly benefited by adequate transfusions, and the signs of failure disappeared as a result.

Downie's (1952) suggestion that administration of large quantities of stored blood might interfere with wound-healing if surgery became necessary has not been borne out by our experience. It is improbable that the requirements of these patients could be met entirely from fresh as opposed to stored blood, however adequate the resources of the transfusion service.

It is not our purpose to discuss the still controversial question of the place of emergency operations in the treatment of acute gastro-duodenal haemorrhage. With the indications previously quoted such operations were performed in 14% of our patients. Mainly through lack of sufficiently vigorous resuscitation, it was impossible to make fit for surgery several other patients who might have profited from it and who died in its absence. We believe that 15 to 20% of the members of a series composed like ours will probably need to be operated on in the acute stage. Our mortality rate of 8.3% in 12 partial gastrectomies—several of which were performed on patients with serious complicating diseases—seems encouraging, and to bear out the statement made by Amendola (1952) that emergency subtotal gastrectomy if performed early may be done without significantly greater risk than the elective procedure. We are prepared to believe that our total mortality rate could have been lowered if we had followed the policy of Stewart *et al.* (1950), who perform emergency gastrectomy on all patients who have had a blood loss in excess of 40% of their V_C. This would have involved operations on nearly 80% of our patients, or about 75 emergency gastrectomies in one year. Emergency surgery on this scale would appear to demand very special facilities, which unfortunately do not at present exist at our hospital.

Comparison with a Control Series

We mentioned above the difficulty of comparing the results yielded by different methods of treatment of acute gastro-duodenal haemorrhage. Nevertheless some standard of comparison is necessary in order to assess the success of any therapeutic regime. For this reason we have analysed a second unselected series of 93 patients with acute gastro-duodenal haemorrhage who were treated at Christchurch Hospital during the eighteen months immediately preceding the introduction of the new regime.

This control series consisted of 68 men and 25 women, with an average age of 59 years; 71% were over 50 and 47% over 60 years. This series was therefore slightly younger than the experimental series. In 86 patients (92.5%) treatment was medical and in 7 (7.5%) by means of emergency surgery. The amount of blood given to these patients varied from 0 to 21 pints (11.9 litres), with an average of 2½ pints (1.4 litres). Half the patients received no transfusions. The distribution of diagnoses was very nearly the same in both series. The mortality rate among the controls was 17.2% (16 cases), with an average age of 64 years. One of the deaths followed emergency surgery.

The experimental and the control series appear comparable as regards age and sex distribution and diagnosis. It is difficult to compare the severity of bleeding as no blood-volume estimations were done on the controls. From a scrutiny of the clinical records it appears, however, that no gross difference existed, and such differences were not in any case likely to be important in what amounts to the two halves of one continuous list of 186 admissions. The two series differ, however, greatly in the quantity of blood which was given to individual patients. Whereas an average of 7.9 pints (4.5 litres) was transfused in the experimental series, the controls received only 2½ pints (1.4 litres), and 50%, among them three fatal cases, were not transfused at all. Five other fatal cases received fewer than 4 pints (2.3 litres) each. The percentage of emergency operations performed on the controls was about half that in the experimental series. We believe that these differences in treatment were probably largely responsible for the reduced mortality rate in the experimental series (7.5% as against 17.2%). This reduction of over 50% in the total mortality is statistically significant ($\chi^2=4.02$; $P<0.05>0.02$).

When comparing our results with those reported in the literature we can take into account only those series which resemble ours in age distribution and severity of bleeding. After a careful search we have found only one report which fulfils these conditions. Tanner (1951) includes in his "Period No. 5" a total of 74 patients 55% of whom were aged over 60 and 34% over 70; 18% of these had emergency operations. The total mortality was 13.5%. In Avery Jones's (1947) series of 411 cases the total mortality was 7.8%. The average age was, however, distinctly lower (33% over 60), although at the time of publication this appeared to be the oldest known series. It was interesting that among Avery Jones's patients 12% of those between 60 and 69 and 21% of those aged 70 and over died. The comparable figures for the present experimental series are 8.3% and 8.6% respectively. We may therefore conclude that our results compare favourably with those of other authors who were working with material similar to that encountered by us. It may also be tentatively concluded that increasing age among patients suffering from acute gastro-duodenal haemorrhage does not necessarily lead to a rapidly increasing mortality rate, provided that the criteria of severity and the methods of treatment are equally applied in all age groups. Of these methods the most important would appear to be early adequate blood transfusion together with emergency surgical operation in suitably chosen cases.

Summary

A method of treating patients with acute gastro-duodenal haemorrhage is described. Its most impor-

tant features are early complete replacement of the lost blood in all patients, and emergency surgical operation in selected cases.

Employment of this method led to a halving of the mortality rate at Christchurch Hospital.

The results in a series of 93 admissions compare favourably with those reported in the literature.

We acknowledge with gratitude the help of Mr. J. T. Murray, hospital biochemist, who standardized and supervised the blood-volume estimations and made many important contributions to our work; and of Drs. A. F. Burry and A. V. Kurta, who assisted throughout the course of these investigations. The following surgeons and physicians were in charge of the patients included in the experimental series: M. H. Aiken, L. A. Bennett, W. H. Bremner, P. W. Cotter, W. M. Cotter, J. K. Davidson, H. E. H. Denham, D. McK. Dickson, M. K. Gray, J. F. Landreth, D. G. Radcliffe, and W. L. F. Utley. Without their help and co-operation this work could not have been undertaken.

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ARSENAMIDE TREATMENT OF FILARIASIS DUE TO W. BANCROFTI AND A. PERSTANS

BY

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Arsenamide is a trivalent arsenical, and has the formula: $(COOH.CH_2.S)_2=As\langle\bigcirc\rangle CO.NH_2$. It was first employed in the treatment of *Wuchereria bancrofti* infections by Thetford *et al.* (1948), when they reported the treatment of six cases. Since then the compound has been used by various other workers as summarized in the discussion below. This paper describes the results obtained in the arsenamide treatment of 37 cases of filariasis in Gambia, British West Africa, and the action of suramin in two trypanosomiasis patients whose blood contained *bancrofti* microfilariae.

Methods.—Four groups of cases were investigated: (1) Two cases of yaws were treated under close observation in the ward as a preliminary test for tolerance. (2) Eleven cases of filariasis were treated in the ward under similar close observation. (3) Twenty-one cases were treated in a village; among these there was one fatality due to acute hepatic necrosis. (4) Five cases were treated in the ward with low doses and special precautions against toxic effects. For the present work the drug was supplied in 5-ml. ampoules of 2.5% buffered solution.

Group 1. Two Cases of Yaws

Case 1.—A man aged 46 complained of pain all over the body. He weighed 60 kg. He was given one intravenous injection of 5 ml. arsenamide, followed the next day by one injection of 7.5 ml. and then 10 ml. daily for 10 days (2 mg./kg. arsenamide, 3 mg./kg., and then 4 mg./kg.). He vomited after the fifth and sixth injections; occasionally a trace of albumin was found in the urine. During treatment he lost 3 kg. in weight, which he subsequently regained. His previous symptoms cleared up.

Case 2.—A man aged 25 had ulcers on the legs and on an arm. He weighed 66 kg. He was given the same injections as in Case 1 (1.9 mg./kg. arsenamide, 2.8 mg./kg., and then 3.8 mg./kg.). He did not vomit at all, but lost 2 kg. in weight, which was regained; occasionally a faint trace of albumin was found in the urine. The ulcers cleared up rapidly.

These cases suggested that 10 ml. of the solution (approximately 4 mg./kg.) daily would be tolerated. The dose level which was adopted for the trial against *W. bancrofti* was half this—namely, 5 ml. (about 2 mg./kg.) daily for 12 days.

Group 2. Cases of Filariasis Treated in Hospital

Eleven cases were treated in the research ward at Fajara. On admission the patients were examined clinically for any contraindication to treatment; and then two or three days were allowed to elapse so that the microfilaria cycle could settle after the change in habits. At 10 p.m. on the evening before the injections of the drug were to begin, two lots of 20 c.mm. blood were taken from the finger-tip and spread on a slide for enumeration of microfilariae in the usual way. Throughout the trial all the slides were examined and the microfilariae enumerated by one of us (J. A. McF.). All subsequent measured quantities of blood in the cases treated in the ward were taken within a few minutes of 10 p.m. Conditions were further standardized by all the injections being given in most cases within a few minutes of 10 a.m. The urines from these cases were examined daily for albumin, each patient was weighed daily, and a watch was kept for any signs of toxicity of the drug, particularly vomiting.

Results

Table I records the microfilariae counts of the 11 patients treated in the ward. Four to five days after the first injection the total number of *bancrofti* microfilariae had decreased by 22%; at nine days it had decreased by 86%; and at 12 days the total reduction was 98%. Subsequently, only occasional microfilariae were found in the blood of these patients. Finally, when the last blood samples were taken (at six months) all the patients were free from microfilariae except for one who still had two microfilariae per 40 c.mm., and one who still had one microfilariae per 40 c.mm. (at three months).

In eight of the patients *perstans* microfilariae were also present initially; 70–200 days after treatment their total numbers were reduced by 70%, and in four the blood became negative.

Toxic Features

Vomiting.—Three patients vomited occasionally. One other patient (Case 10) vomited a quarter to three hours after each injection; she was receiving the largest dose per kg. of body weight, and treatment was stopped.

Headache (4 cases).—This is difficult to assess, as it is a common complaint among Africans.

Signs of Death of Adult Worms or Allergic Reactions.—Two patients had pyrexia. One other patient developed enlarged tender glands in the axilla and one developed a tender epididymis.

Loss of Weight (1 case).—This was the patient (Case 10) who vomited considerably.

TABLE I.—*Treatment of* 11 *Cases of Bancroftian Filariasis* (*Group* 2) *in Hospital by Arsenamide, 125 mg. Daily*

Case No.	Age	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (*M. perstans* in parentheses)							
				Start	Day 4–5	9	12	26	40–60	70–100	200–250
1	28	55	12	67 (115)	48 (67)	9 (58)	4 (62)	4 (53)	0 (23)	0 (39)	—
2	50	55	12	40 (124)	26 (125)	6 (125)	5 (98)	1 (167)	0 (46)	0 (50)	—
3	30	65	12	399 (4)	461 (8)	72 (7)	7 (11)	1 (8)	4 (4)	1 (4)	—
4	40	58	12	73 (63)	63 (70)	10 (73)	0 (30)	0 (39)	0 (37)	—	0 (10)
5	17	42	12	302 (7)	336 (10)	31 (4)	0 (5)	0 (0)	0 (0)	0 (1)	0 (0)
6	40	62	10	459 (41)	—	24 (49)	0 (25)	—	1 (11)	0 (6)	0 (0)
7	18	61	12	580 (19)	454 (14)	107 (10)	24 (6)	—	4 (3)	0 (1)	0 (0)
8	16	49	12	808	518	75	3	—	1	1	0
9	50	48	12	231 (1)	107 (0)	76 (2)	9 (0)	—	0 (0)	2 (0)	2 (0)
10	50	41	9	117	22	—	0	0	—	0	0
11	25	54	12	103	75	—	1	0	0	—	—

The days are recorded after the first injection. Cases 5 and 10 were females, the rest males.

Damage to Liver (1 case).—In one patient (Case 6) the temperature rose, finally reaching 104° F. (40° C.) after the tenth injection; two days later he vomited repeatedly; and the next day he developed jaundice, with bile and albumin in the urine. He made a satisfactory recovery, and one month later was much improved. It was difficult to assess the cause of the jaundice, as it was possible that there was either previous liver damage or a coincidental infective hepatitis, both of which are fairly common in Gambia. Since the patients previously treated had showed no other toxic features the trial was continued; and subsequently five more cases were treated satisfactorily in the ward.

Albuminuria did not occur in any of the patients, apart from the one case noted above.

Group 3. Cases Treated in a Village

Twenty-one cases of filariasis were selected for treatment in a village which had been previously surveyed. Heavy infections were chosen. Each patient was examined clinically. The projected dose schedule was a daily injection of 5 ml. for 12 days. Since the lowest weight of any patient selected was 50 kg. no patient received a dose greater than 2.5 mg. of arsenamide per kg. daily. After the group had received 10 injections, however, treatment was discontinued because one of the patients died (see below). The injections were given between 6 and 7.30 p.m., after the villagers had returned from their work in the fields. They were given intravenously and slowly with the patients lying down. Urine specimens were examined for albumin before treatment, and 3, 6, 9, and 15 days after the first injection. All patients were weighed before and after the course of injections. On the evening before the injections were begun, measured quantities of blood were taken as described above, between the hours of 10 and 11 p.m. Any information on toxic features volunteered by the villagers was recorded, and direct questions were asked only after the course was completed.

TABLE II.—*Treatment of 21 Cases of Bancroftian Filariasis* (*Group 3*) *in a Village*

Case No.	Age	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (*M. perstans* in parentheses)					
				Start	Weeks				
					2	5	12	17	30
14	35	65	10	228	0	1	0	0	0
16	38	56	10	52	0	0	0	0	0
17	40	70	10	65	0 (1)	0	0	0	0
18	37	67	10	185	0	0	0	0	—
19	21	31	10	132	0	0	0	0	0
20	60	62	10	141	0	0	0	0 (1)	0
21	45	68	10	284 (1)	0 (2)	—	—	—	—
22	50	61	10	35	0	0	0	0	0
23	40	31	10	116	0	0	0	0	—
24	35	61	10	166	0	0	0	0	0
25	35	50	10	141	0	0	0	0	0
26	25	64	10	21 (67)	0 (3)	0 (7)	0 (2)	0 (6)	0 (0)
27	28	65	10	263 (9)	1 (4)	1 (4)	0 (3)	0 (2)	0 (3)
31	50	67	10	59	0	0	0	0	0
32	35	52	10	652	0	0	0	0	0
28	36	58	10	1,337	0	0	—	0	0
29	55	50	9	64	0	0	0	0	0
30	18	63	9	132	0	0	0	—	—
13	36	61	8	230	0	0	0	0	0
15	35	50	5	834	0	0	0	0	0
12	55	53	3	19	Dead				

The weeks are recorded after the first injection. Cases 13, 15, 19, 20, 23, 25, and 32 were females, the rest males. The dose was 125 mg. arsenamide per patient daily.

Results

Table II records the microfilariae counts of these patients. In all the blood samples taken two weeks after the first injection, only a single *bancrofti* microfilaria was found. Sixteen of these patients had received 10 injections of arsenamide, but 2 had 9 injections, 1 had 8, and 1 had only 5. Seven months after treatment the blood of all the patients was free from *bancrofti* microfilariae. Two of these patients also contained appreciable numbers of *perstans* microfilariae in the blood; one patient became negative.

Toxic Features

Vomiting (7 cases, 33%).—One patient vomited after each injection, while the others vomited only occasionally.

Diarrhoea.—Four people complained of occasional loose stools during the course of injections. This feature is difficult to assess; it was not noted in the cases treated in the ward.

Dizziness occurred in two cases.

Generalized Pain.—One person complained of pains all over the body. This is a common complaint in Africans, and was probably associated with yaws.

Signs of Death of Adult Worms or Allergic Reactions.—One person developed a filarial abscess on the medial aspect of the thigh which subsequently broke down and discharged thick creamy pus; one developed a bilateral hydrocele; one had a transient enlargement of the scrotum; one had an enlargement of the epididymis. Several days after the injections had ceased one person developed weals on the skin associated with pruritus which cleared satisfactorily with mepyramine maleate.

Loss of Weight.—One person lost 3 kg. (associated with vomiting) and one lost 3.5 kg. (not associated with vomiting).

Signs of Liver Damage.—One man died from liver damage after receiving only three injections of the drug; this case is described in detail below. Another man developed jaundice four and a half weeks after the last injection; a fresh dry sterilized syringe and needle had been used for each injection, so this jaundice could not have been due to the passage of a virus.

Albuminuria did not occur in any case. The drug did not leak from a vein on any occasion.

The Fatal Case

The patient, a man aged 55, weighed 53 kg. He was given three daily injections of 5 ml. (2.4 mg./kg.). After the third injection he vomited and complained of vague retrosternal pains. The symptoms were mild and hardly seemed sufficient to contraindicate further treatment; but no more injections were given. Two days afterwards he felt well; but later that night developed pain in the back of the neck, staggered, and was unable to stand or sit up. This was reported next day, when the investigator returned to the village and found that the patient was comatose.

On admission to the ward he was still comatose but able to move his limbs. Reflexes were present and normal. Lumbar puncture showed: no increased pressure, Queckenstedt's test normal, Pandy's test positive, 60 lymphocytes per c.mm. No trypanosomes seen. Blood pressure, 230/120 mm. Hg. Urine contained no albumin or bile. There was some doubt whether or not he had a slight icteric tinge, but African observers considered that the colour of his conjunctivae was normal. Dimercaprol and penicillin were given, but he developed the signs of basal pneumonia and died four days later.

Post-mortem Findings.—The liver weighed 880 g. and was stained yellow, the kidneys 170 g. each, and the heart 284 g.; there was some atheroma of the heart and aorta. The urine contained no appreciable amounts of bile salts or pigments. *Histology.*—In the liver were numerous areas of recent focal damage from which most of the parenchymal cells had disappeared; there was considerable proliferation of fibroblasts, but no evidence of pre-existing cirrhosis. In the kidneys, the cells of the cortical nephrons showed the appearance of massive necrosis (part of this appearance could have been due to post-mortem autolysis); many of the medium and small arterioles showed medial fibrosis and irregular intimal thickening. It is concluded that death was due to widespread necrosis of the liver.

Group 4. Cases Treated with Low Doses in Hospital

The experience with the fourth group of patients indicated that although large doses of arsenamide were therapeutically effective they might also have dangerous toxic effects. Accordingly an investigation was made to discover whether a much lower dose, which would be small enough to be safe, might yet be sufficient to produce cure. For this purpose five patients were treated with strict precautions against toxic effects—namely, the dose was 0.3 mg./kg. daily (only one-eighth of that previously used), the patients were kept under careful supervision in hospital, and they were given 50 g. of dry skim-milk daily (protein-rich supplement) in addition to good hospital diet, so as to fortify the liver against the toxic effects of arsenic. No toxic effects were observed; and the therapeutic results are shown in Table III. Reduction of the microfilaria count was much slower than it had been with large doses. Of the four patients who could be followed for five months the count was greatly reduced in two cases and probably the microfilariae will eventually disappear; in one case the count fell to a quarter of its original level, and in one case there has been no appreciable change. Thus the filaricidal effect of 0.3 mg./kg. daily, although considerable, is not completely satisfactory. From this small group of patients it might be deduced that 0.6 mg./kg. would be the minimum effective dose.

TABLE III.—*Treatment of 5 Cases of Bancroftian Filariasis (Group 4) with 0.3 mg. Arsenamide per kg. Daily*

Case No.	Age in Years	Weight (kg.)	No. of Injections	Bancrofti Microfilariae per 40 c.mm. (*M. perstans* in parentheses)			
				Start	Day 14	80	155
33	26	54	14	83	112	26	17
34	24	51	14	52	65	66	3
35	15	37	14	13	12	5	1
36	9	25	14	111	131	120	102
37	40	48	14	104 (58)	54 (21)	—	—

Case 35 was male, the rest females.

Treatment with Suramin

Suramin is very effective for the treatment of onchocerciasis, in which it kills the adult worm (Wanson, 1950). As regards its action on *W. bancrofti*, we have not found any reports which include an adequate follow-up of the patients for several months, to see whether the microfilariae disappeared. Such late disappearance would suggest that the adult worms had been killed or sterilized. Accordingly the opportunity was taken of observing the action of suramin in two patients with trypanosomiasis whose blood also contained *bancrofti* microfilariae.

Case A.—A man aged 45, weight 60 kg., was given 1 g. of suramin intravenously on December 18, 21, and 23 and January 1 and 9 (total 5 g.). At 10 p.m. on December 18 his blood contained 7 microfilariae per 40 c.mm.; on March 7 (79 days after the first dose), 57; and on May 28, 62.

Case B.—A woman aged 35, weight 50 kg., received three intravenous doses of 1 g. of suramin between December 18 and January 4; and on January 9, 1 g. At 9.30 p.m. on January 9 her blood contained 23 microfilariae per 40 c.mm.; on March 7, 11; and on May 28, 10.

In these two cases there was no evidence that suramin was able to kill or sterilize the adult worms of *W. bancrofti*. Wanson (1950) states that it does not kill the adults of *W. bancrofti, Loa loa, Acanthocheilonema perstans,* or *A. streptocerca,* although no evidence is given for this statement. In our laboratory at the National Institute for Medical Research, in London, suramin had no lethal action on *Litomosoides carinii*. Clearly the chemotherapeutic reactions of filarial worms differ according to the different species.

Discussion

The action of a chemotherapeutic drug must be considered from two aspects, that of the parasite and that of the host—that is, therapeutic action and toxicity.

Therapeutic Action

Arsenamide in high doses (2 mg./kg. daily) causes disappearance of the microfilariae of *W. bancrofti* from the blood within two weeks. Since this period is much less than their normal life span, their disappearance must be directly due to a lethal action of the drug. Such an action has been demonstrated *in vitro* in concentrations of approximately one in a million (Hawking, 1950). (The gradual disappearance of the microfilariae after small doses (0.3 mg./kg.) was presumably due to failure of replenishment after death of the adult worms.)

Since the disappearance of microfilariae caused by arsenamide is permanent (more than seven months, at least) there is evidence that death or permanent sterilization of the adult female worms has been brought about: on general grounds, and by analogy with the experimental findings with *Litomosoides* in cotton rats, it is almost certain that the adult worms have been killed. This effect is produced by doses of about 1 to 2.5 mg./kg., usually given daily for 15 days. Thus Thetford *et al.* (1948) and Otto *et al.* (1952, 1953) gave 1 mg./kg. for 15 days. In the present series the number of injections varied from 5 to 12 (9 patients received 12 injections, 17 received 10, 3 received 9, 1 received 8, and 1 received 5). Since the daily amount given was not calculated on a weight basis, the actual dose varied from 1.8 to 2.5 mg./kg., according to the weight of the patient. All the courses of injection were effective in removing microfilariae from the blood. With much smaller doses (0.3 mg./kg.) the antifilarial effect, although considerable, is not complete. Perhaps the minimum curative dose is about 0.6 mg./kg.

Arsenamide also causes considerable reduction in the number of *M. perstans* microfilariae in the blood. It is possible that arsenamide kills many of the adult worms of *A. perstans,* although a long period of observation might be necessary to obtain evidence of this, since these microfilariae may live over two and a half years in the absence of the adult worm (Gönnert, 1942). As this parasite is non-pathogenic, however, such action is of academic interest only.

Toxic Action

As described above, intensive treatment with arsenamide may produce various minor toxic effects—for instance, vomiting, dizziness, headache, loss of weight, and (possibly) diarrhoea. Localized inflammation or allergic reactions due to the death of adult worms may also develop during treatment. All these, however, are overshadowed by the

tendency of arsenamide to cause damage to the liver, which may proceed (as in the case described above) to fatal necrosis. In the present series of 35 patients treated with doses of 1.8 to 2.5 mg./kg. a day one patient developed pyrexia after the tenth dose, and jaundice appeared three days later; one man developed jaundice about four and a half weeks after the last of 10 injections (the relation of this to the treatment is not clear); and one man suffered fatal necrosis of the liver three days after receiving three doses of 2.4 mg./kg., total 7.2 mg./kg. Ampoules from this batch of material were returned to the manufacturers. Chemical examination revealed no alteration of composition, and biological assay showed no increase of toxicity. Therefore the toxic effect on the liver must be due to the unchanged compound, probably to the arsenic part of the molecule; there is no reason for believing that the benzamide part of the molecule has any significant toxic action.

There had been considerable previous experience with this compound, and many patients had tolerated much greater total dosages without ill effects. Thus Murgatroyd (1937) administered it (under the name K324) to eight patients with sleeping sickness in the Gambia in doses as high as 35 mg./kg.; doses greater than 2.5 mg. produced vomiting, abdominal pain, or diarrhoea, and in one case there was severe jaundice. Thetford *et al.* (1948) and Otto *et al.* (1952) treated 18 cases of filariasis with doses of 1 mg./kg. daily intravenously for 15 days and observed only minor toxic reactions. Similarly, Otto *et al.* (1953) treated a further 15 cases with the same dose schedule. The main toxic features observed were diarrhoea and nausea; one case had severe lymphadenitis. Hawking (1950) treated four patients with daily injections of 100 or 150 mg. for seven days—that is, 1.7 to 2.5 mg./kg. The larger doses were followed by vomiting and diarrhoea, but there was no suggestion of liver damage. In East Africa 36 cases have been treated with doses of 1 mg./kg. daily for about 14 days; one case of jaundice occurred (Filariasis Research Annual Report, 1952). We have also heard privately of two cases of non-fatal severe hepatitis with jaundice which occurred in the West Indies after treatment with arsenamide. No evidence of special toxic action on the liver of rabbits, dogs, or monkeys was seen by Otto and Maren (1950), or by Drudge (1952), who gave dogs 2.2 mg. of arsenamide per kg. intravenously daily for 15 days.

Apparently the death described above was another example of the tendency of arsenic compounds to cause extensive necrosis of the liver in a very small proportion of the cases treated with it. Such subjects must be predisposed to this damage by accessory factors, but the nature of such factors and the causation of widespread liver necrosis in man are still largely unknown. The possible accessory factors include:

(*a*) *A Virus Infection, Latent or Incipient.*—Hepatitis, presumably infective, certainly occurs in Gambia, since several Europeans developed it recently. In the present investigation a clean sterile syringe and needle were used for each injection, so there was no possibility of passage of infection by this means; moreover, the incubation period was much too short for viral hepatitis to develop from the patients' injections.

(*b*) *Lack of Essential Nutrients, Especially Tocopherol and Cysteine.*—This food deficiency causes hepatic necrosis in rats (Himsworth, 1950). Many Africans are certainly malnourished, but there is no evidence that the state of nutrition of the present patient was worse than that of others in the same village who were treated. However, in any further trials with arsenical compounds it would be advisable to take the precaution of fortifying the liver against such toxic action by giving a protein-rich supplement—for example, 50 g. dried milk daily in addition to the usual food.

It is concluded that arsenamide, in daily doses of 1 mg. or more per kg. for 10 to 14 days, is an effective drug for the sterilization of bancroftian infection in patients, and that its use is not devoid of risk. Since filariasis is not a fatal disease, it is accordingly not justifiable to use arsenamide for general treatment. In any further investigation of this drug careful precautions should be taken to avoid damage to the liver: the dose should be kept low, preferably below 0.6 mg./kg.; the patients should be treated in hospital under strict medical supervision; and the protein content of the patient's diet should be increased—for example, 50 g. of skim-milk powder daily in addition to a good general diet—in order to fortify the liver, the protein supplement being given for three days before, during, and three days after treatment.

Summary

Thirty-two cases of filariasis due to *W. bancrofti* were treated with arsenamide (*p-bis*-(carboxymethylmercapto)-arsino-benzamide). The dose was 125 mg. (1.8–2.5 mg./kg.) daily by intravenous injection, usually for 10–12 doses.

This treatment removed most of the microfilariae of *W. bancrofti* from the blood within two weeks after the first dose, and all but two of the patients were free from microfilariae six months later. It is concluded that the treatment killed or sterilized the adult worms; it also killed many of the microfilariae (and the rest disappeared in the absence of adult worms to replenish their numbers). The treatment also caused a significant reduction in the number of *A. perstans* microfilariae present, indicating a filaricidal action on this worm also.

The drug undoubtedly has a toxic effect upon the liver. In two cases the treatment was followed by jaundice, three days and four weeks respectively after the last injection; and one patient developed fatal necrosis of the liver after having received only three injections. Other minor toxic effects included vomiting, dizziness, headache, and loss of weight. A few patients showed localized inflammation or allergic reactions, apparently around worms which had been killed.

Five more patients were treated with much lower doses (0.3 mg./kg.) daily for 14 days under strict medical supervision, and with a protein-rich supplement to fortify the liver. No toxic effects were observed. Among the four patients who were followed for five months the microfilaria count was reduced almost to zero in two, it fell to a quarter in one, and it remained unchanged in one. Perhaps the minimum curative dose is about 0.6 mg./kg.

Arsenamide in doses of 1–2 mg./kg. daily is a potent filaricidal drug against *W. bancrofti*, but the danger of severe toxic action upon the liver is a contraindication to its use except under special conditions.

Two patients were treated with 4 g. and 5 g. respectively of suramin for trypanosomiasis. This treatment had no apparent effect during the next five months on the number of *bancrofti* microfilariae in their blood.

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A BIOLOGICAL APPROACH TO MEDICAL GEOGRAPHY*

BY

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Everyone knows that frost-bite occurs at the North Pole and heat exhaustion is more common in the Tropics. There is a tendency to look upon medical geography as merely an elaboration of this simple theme, but it is not merely a descriptive subject: it is a most fascinating part of human ecology or social biology—the vitally important sphere of human natural history to which geography is an essential background.

The method of approach followed in this paper was indicated by studies of the medical geography of scrub-typhus made in India and Burma during the war and followed up in Malaya (Audy, 1947; Audy and Harrison, 1951). An attempt is made to apply the ideas and methods of the biologist to the problem, with the support of facts gained by recent studies of animal parasites. The main object here is to stress the contribution that can be made by studying assemblages of parasites as a whole; it is therefore concerned almost entirely with diseases caused by organisms.

The term "parasite-pattern" is used here to describe the whole assemblage or array of parasites (including all pathogens) which are associated with a host population being discussed. By extension of this meaning, I also speak of the "pattern" of disease caused by some of the parasites. My object is to relate the parasite-patterns of various communities to those elements of human existence and behaviour which themselves reflect the geographical background in one way or another. To complete the associations I here call the relevant elements of existence and behaviour of a community its "social-pattern."

Patterns of Disease in Somaliland

I will first consider the semi-desert and thorn-scrub of Somaliland. There are great stretches of sparse grassy plains or thorny scrub with widely scattered water-holes. This sort of country must evoke a distinct type of response from the primitive community which first occupies it. It sets a low limit to the overall population, which is almost entirely pastoral and supported by drought-resisting beasts of burden and livestock, such as camels and mules, goats and fat-tailed sheep. The community soon learns that it cannot continue grazing its animals in one place. Not only is it forced to discover and use seasonal grazing areas, but this together with the scarcity of water will also encourage a natural tendency to form well-knit tribes, with tribal grazing areas and some sort of portable villages composed of tents or their equivalent, which can easily be folded up and taken elsewhere. Naturally, the use of such portable huts, which in Somaliland are small hemispherical cocoons of matting, encourages sleeping in a compact huddle. In such ways the geography of the place has a tremendous influence in guiding the pattern of existence of the community or what in this paper is referred to as the social pattern.

Linked to this social pattern in response to a particular and exacting environment is the pattern of disease. Relatively few rural diseases occur in Somaliland, but, as would be expected, there is a pattern related directly to the habitat. Malaria is highly seasonal and highly localized, spreading outwards from small foci during the short rainy season. The general standard of nutrition is low and outbreaks of nutritional disorders occur in bad years. The incidence of desert sores following minor injuries, often leading to severe crippling, is high. In addition to the desert sores, there is a moderate incidence of mycetoma (Madura foot), the fungal spores being inoculated into the skin by the thorns and similar parts of plants on which the fungus concerned appears to grow naturally. Cataract and eye infections are associated with the flying sand and glaring sun, as well as with the flies which thrive in villages. The very free breeding of the flies is directly related to the dry climate. The presence of numbers of soft ticks carrying relapsing fever is also related to the climate. So also is the presence of many herds of animals, including packs of jackals and hyenas, among which rabies is permanently established.

Heavy and regular rainfall has a general cleansing effect which has not yet been properly assessed. Its absence in Somaliland may help to account for much of the spread of intestinal and respiratory infections as well as for the zymotic diseases. The intense dryness and frequent sand-storms encourage sore throats, which the Somalis have been led to treat heroically by snipping off the uvula, usually with slender home-made scalpel and a sharp hook made from an umbrella-rib. Respiratory infections, including tuberculosis, are encouraged by the huddling together in the tiny portable huts, while their effects are made worse by malnutrition.

Malaria in Ceylon

It would be desirable to draw parallel pictures of other places, but these pictures rapidly become much too complicated. I now turn to single diseases in particular places. Malaria offers countless illustrations of medical geography. Ceylon has a particularly fascinating malarial history, culminating in the mastery of epidemic malaria in recent years by a well-planned D.D.T. campaign. The vector mosquito is not very efficient and requires to be present in relatively large numbers for successful transmission. It breeds in clean open pools and puddles, especially in stream and river beds. When these biological requirements are imposed on the geography of the island a very distinctive and peculiar malarial pattern results.

A central mountain-mass breasts the prevailing monsoons and encourages heavy rainfall in the south-west quadrant of the island. Most of the island, however, has a very dry season. Malaria in this "dry zone" is perennial and there is a regular malaria season during the rains. By contrast, the lush, densely populated wet zone in the south-west offers little to the vector mosquito and it is curiously free of malaria in ordinary years. Occasionally during exceptionally dry years certain rivers almost dry up, forming extensive chains of pools in which the vector breeds by the million. This led to violent epidemics in the non-immune population—such as that in 1934–5, when over 80,000 deaths were attributed directly to malaria. Man has aggravated this situation by extensive deforestation in the hills, which results in less retention of water in the catchment areas and tends to produce more rapid changes of water-level in the rivers with more frequent pool-formation during dry spells.

The Typhus Fevers

The next example is the typhus fevers, caused by rickettsiae and transmitted by insects, ticks, and mites. These rickettsiae fall into three groups. The two most primitive groups, carried by ticks and mites, cause infections of small mammals and their parasites, and are only accidentally conveyed to man by a few of these parasites when he loiters in infested places. The vectors are restricted in their distribution in two ways: firstly, on a small scale to patches or "islands" such as a particular stretch of a valley or a single field; and, secondly, on a large scale to geographical regions where conditions are generally favourable for the development of the vectors. Ticks abound in drier tracts outside the rain-forest, so that tick-typhus is practically confined to such country. The mites which carry

*Based on a lecture on the geography of disease given at the University of Malaya in January, 1952.

scrub-typhus have their home in south-east Asia, where they now abound in the rat-infested scrub which follows deforestation. Scrub-typhus is confined by what are probably formidable barriers to the further spread to the vector—by tropical deserts, ice deserts, and great mountain ranges on the mainland, by extensive oceans which have almost stopped spread elsewhere, and by excessive dryness which has hindered all spread beyond a very small part of tropical Australia.

An interesting feature of both tick- and scrub-typhus is that the disease shows definite changes in character and severity from place to place. This can be correlated with serological types of the rickettsiae concerned. This is most pronounced with tick-typhus, in which local characters have given rise to a larger number of place-names for different forms.

The third group of rickettsiae is distinctive by having become adapted to life in the guts of insects. Flea-typhus, the more primitive member, is carried by various rat-parasites and transmitted to man by the same rat-fleas as carry plague. Because the domestic rat and its fleas are concerned, flea-typhus is urban and almost cosmopolitan in its distribution. In the most recently evolved member of this group, the flea-borne rickettsia has become adapted to the human body-louse. This at once results in three things: firstly, a restriction to cold climes or high altitudes, and cold seasons; secondly, a tendency to spread from man to man in the form of a swift epidemic; and, thirdly, an extension into regions where the rat-flea has no influence. Although both flea-typhus and epidemic or louse-typhus are essentially urban, the requirements of the vector have shifted the distribution of louse-typhus away from the equatorial belt and far into and beyond what Marston Bates calls the Intemperate Zones.

Parasite-patterns of Animals

These examples have been treated superficially. A deeper study confirms that there are important relations between the entire disease-pattern of a community and its geographical background. Recent investigations in Malaya have given some useful facts with which to approach this problem. Nearly 20,000 animals and their parasites, from forest, scrub, plantations, and towns, have been studied in Malaya since 1947 (Audy and Harrison, 1953). One of several objects of this study was to investigate the parasite-patterns of these animals and to attempt to use the parasites as "ecological labels" (Audy, 1947). The parasites concerned are all those viruses, bacteria, protozoa, fungi, worms, and arthropods which live on or in or at the expense of higher organisms such as the vertebrates, whether harmlessly or harmfully. At a rough estimate there are perhaps 50,000 known species of these parasites potentially able to parasitize the vertebrates, including man. Although very many parasites are available, the whole population of any host in any locality usually supports only a few dozen. The assemblage of these commoner parasites, of various kinds and in varying numbers, constitutes a pattern. I am concerned with the reasons why these patterns differ among themselves in different communities and why they involve but a fraction of the available parasites.

The tree-living squirrels in the Malayan rain-forest support some 30 species of parasitic mites which together make up a pattern broadly characteristic for these squirrels. Ground-rats which live in the same area have quite different parasite-patterns. There is a rat (*Rattus canus*), however, which has a pattern essentially like that of the tree-squirrels and unlike that of the ground-rats. A correct inference from this is that *R. canus* lives in the trees like the squirrels. The picture is completed by the ground-squirrels, whose parasite-pattern is like that of the ground-rats. There is reason to believe that other groups of parasites would give more or less similar contrasting patterns, and would suggest that the parasite-pattern is directly related to the environment, to the conditions of life, and to the way of living of the host.

This supposition is supported by the parasite-patterns found in certain rats. Three of these rats are very important commensals* of man in Malaya. They are either absent from or rare in the native forest but occur in great numbers in conditions created by man following deforestation and settlement. These three rats are the Malayan wood-rat (*Rattus rattus jalorensis*), the field-rat (*R. r. argentiventer*), and the house-rat (*R. r. diardii*). Although all the parasites of these rats are completely interchangeable, each kind of rat supports a distinct assemblage of parasites; each has a parasite-pattern of its own. This is entirely owing to the fact that these particular rats are living in different conditions—the wood-rat in oil-palms, the field-rat in grassland, and the house-rat in towns. In other words, the differences in parasite-patterns are related to small-scale geographical differences. A fourth rat, *R. r. jarak*, comes from an uninhabited island, Jarak, in the Malacca Straits. This rat is virtually an escaped house-rat, introduced long ago to the island and running wild on the forest floor. In the absence of predators and competition, the Jarak rat has overpopulated the island and is unusually heavily infested by worms and other parasites (Audy *et al.*, 1950). However, the parasite-pattern of the Jarak rat is found to be of the same type as that of a typical forest rat, *R. mülleri*.

Geographical Background and Disease-patterns in Man

The example given by these rodents establishes an important point of view. What has been illustrated by rats applies directly to man. Soil and vegetation are decided originally by climate and geology, and the vegetation and climate together decide the structure of the animal communities that will be found. If man appears on the scene, the climate, vegetation, and soil, and to a varying extent also the animal life, play a great part in deciding for him how his social pattern is to develop; how he will grow or hunt his food; how much clothing he will wear; what sort of shelter or house he will build; whether or not he will be subject to catastrophes such as floods or erosion or drought or the choking up of his clearings by intractable weeds; and whether or not he will wander about or remain to form either compact or scattered settlements. As his social pattern develops, his pattern of parasitism becomes established, and in these early stages the whole complex is related to the geographical background.

Man immediately starts altering the geographical background—for example, by widely destroying the vegetation. So his social-pattern and his pattern of diseases gradually change, but, even so, they are related to the environment. The change is largely one of emphasis.

The disease-patterns are, of course, greatly modified by various purely human social elements. Religious taboos relating to food affect the incidence of tapeworm; religious fasting may add to the effects of undernourishment. Schistosomiasis in the Yemen is almost confined to the ritual ablution pools in mosques (Kuntz, 1952). Social elements have a tremendous influence on the pattern of expression of all the treponematoses. The "civilization" of many communities, or the introduction to them of many outsiders with a higher standard of living, may unmask infections which have hitherto saturated the communities and kept up a general standard of immunity dating from childhood. Poliomyelitis and the viral encephalitides are important examples; in certain circumstances malaria is another example. Finally, a peculiarly human element is introduced by urbanization.

In due course there is always more or less urbanization of the community, and at the same time more frequent and wider traffic with other places. Many diseases, especially epidemic diseases, appear by introduction from areas which may be remote, to be added to a distinct urban pattern of disease. Traffic between urban centres leads to a dispersal

*Commensals include organisms and creatures that "parasitize" the nests of hosts or other parts of the environment which the hosts have characteristically modified, rather than the bodies of individual hosts.

of diseases and a tendency for urban patterns to be similar over very wide areas. Many urban epidemics tend to involve the rural population secondarily. Finally, there may be industrialization, which evokes its own elements in the disease-patterns. These industrial diseases are, like the rural diseases, often very closely related to the geographical background: an example is the pneumoconioses, which are related to the geology.

Conclusion

In developing our approach, the attention to assemblages rather than to individual parasites or diseases is very important—it would be described by the biologists as a synecological approach, concerned with the functional setting of organisms in relation to the other organisms, as opposed to an autecological approach, concerned with a single organism and its relations with the environment. Several workers have drawn attention to the pathology of social groups in their entirety. Ryle (1948) approached social pathology with the experience of a clinician: he rightly looked upon society as an organism which may be approached as such by the clinician as well as by the pathologist, the epidemiologist, and the psychiatrist.

Those who are sympathetic towards the philosophy of holism expounded by General Smuts (1936) will at once see that the synecological approach is also holistic. The lesson is that as soon as components have been sufficiently studied in isolation, they should then be set provisionally into their organized system or pattern and that the system should be studied as an organism in its entirety. Taking the analogous parasite-patterns of rodents, we have been enabled, from anomalies appearing in the patterns, to make inferences and plan investigations which would not otherwise have occurred to us. These anomalies could be detected only by studying the patterns as patterns and not by studying isolated parasites.

Summary

The whole assemblage of diseases from which a community suffers forms a pattern which can profitably be viewed as a whole. Those diseases caused by organisms form part of a general parasite-pattern. With examples of such patterns drawn from studies of rodents in Malaya, the parasite-patterns are considered to be decided largely by environment—that is, by the geographical background (which may be taken on a very small scale).

The distribution of diseases in different communities in different places is approached by a holistic study of the relationship borne by the entire disease-patterns of the communities to the social patterns and the geographical background. As a simple example, it is suggested that the disease-pattern in Somaliland is more or less evoked by the geography of the country. Further illustrations are drawn from malaria in Ceylon and from the typhus fevers.

In the earliest stages of man's occupation the link between geography and the disease-pattern appears to be very close. Man soon alters his environment, but the disease-patterns, while changing also, are still related broadly to the environment, and the change is largely one of emphasis. Urbanization, however, evokes urban patterns of disease, which tend to be widely distributed and uniform in nature, largely by interchange between urban environments, which are essentially the same everywhere. Industrialization evokes new elements, which again may become closely linked to the geographical background.

The methods and aims of medical geography, or medical ecology, are of interest even to those concerned with preventive medicine in the most urbanized or stereotyped environments. A particular biological approach is here added to those which are already familiar.

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HAEMOLYTIC DISEASE OF THE NEWBORN CAUSED BY A NEW Rh ANTIBODY, ANTI-C^x

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Haemolytic disease of the newborn commonly occurs in Rh-negative women who are delivered of Rh-positive children, where the mother has Rh antibodies in her serum. Cases are also seen in which Rh-positive mothers are delivered of children affected with this disease; in the majority of such cases the maternal serum contains Rh antibodies anti-E or anti-c. Antibodies to other blood-group antigens—for example, anti-Kell—may also be present in the maternal serum and give rise to this condition. Occasionally, haemolytic disease of the newborn is caused by antibodies to much rarer blood-group antigens; these may belong to the Rh series—for example, C^w—but a number of cases have been described in which the cause has been a family antigen.

The family antigens appear to be of two kinds—those which have been observed because they have given rise to haemolytic disease of the newborn, and those which have been found within a family but are not associated with the occurrence of this disease. Those which have caused haemolytic disease of the newborn have been described by Levine *et al.* (1951) (Miltenberger); by Holman (1953) (Wright); and by Davidsohn *et al.* (1953) (Berrens). These blood groups are confined to the members of the family in which the case of haemolytic disease of the newborn occurred.

The present case occurred in a third pregnancy, and was originally thought to be due to a family antigen, but subsequent investigations suggested that it was, in fact, a rare Rh agglutinogen at the C-c locus, C^x. It is proposed in this paper to describe the clinical history of the case and certain serological findings, and to discuss their importance. Detailed serological work and family studies will be described in full elsewhere.

Clinical History

The mother had had two previous pregnancies: in 1947 a full-term normal male child, who is alive and well; and in 1950 a 7-months pregnancy resulting in a stillbirth.

In 1953 a full-term male child, weighing 8 lb. 2 oz. (3.7 kg.), was delivered normally. The child was jaundiced at birth, but this had faded by the third day. He was artificially fed and gained weight normally. He vomited twice during the first week of life, and on the tenth day was noticeably

paler. When 15 days old he vomited and was noted to be very pale and slightly icteric, and showed reluctance to feed. There was no pyrexia or evidence of infection; stools and urine were normal; there was no external bleeding or any signs of internal bleeding. On the 18th day he was admitted to St. Mary's Hospital under the care of Dr. G. Komrower, when he was found on examination to be pale, slightly icteric, and lethargic.

The umbilicus was healthy, and examination of the abdomen revealed enlargement of the liver and spleen three fingerbreadths below the costal margin. No abnormality was detected in the heart and lungs; eyes, head, ears, mouth, and palate were normal. No abnormality was detected in the central nervous system. There were no congenital abnormalities. The blood count was: red cells, 1,200,000 per c.mm.; Hb, 22% (3.3 g.); C.I., 0.91; white cells, 9,000 per c.mm.; normoblasts, 80 per 100 white cells, some showing mitosis. The direct Coombs test on the child's cells was positive. The Wassermann reaction carried out on the mother's blood was negative, and antenatally her blood had been typed as Rh-positive.

A transfusion of 60 ml. of compatible whole citrated blood was given when the child was admitted, and the haemoglobin rose to 43%. On the 19th day after birth 90 ml. of group A Rh-positive compatible blood was transfused, and the haemoglobin increased to 59% (8.7 g.). On the 20th day the direct Coombs test was negative, and a further 100 ml. of blood was given; on the next day the haemoglobin was 72%, and the child was much improved. By the 26th day the haemoglobin had dropped to 63% (9.3 g.); 120 ml. of blood was given on the 27th day, and again five days later. The haemoglobin was now 93% (13.6 g.), and after this the child progressed well, and when 6 weeks old was in good health, both liver and spleen being impalpable.

Materials and Methods

Blood samples were obtained occasionally as citrated blood, but largely in the form of clotted blood; all random blood samples were obtained as clotted blood.

Methods.—Saline and albumin agglutination tests and titrations and the antiglobulin (Coombs) test were performed according to the techniques suggested by the Medical Research Council (1952). Papainization of the red cells was performed by the method described by Stratton (1953) slightly modified in order to increase the degree of papainization of the erythrocytes.

Serological Findings

Family Blood Groups

Below are shown the blood groups of the mother, the affected child, the father, and the healthy child of the family in which this case of haemolytic disease occurred:

Mother:	A_1	R_1R_2 (CDe/cDE)	M.S	P+	Le(a−b+)	Lu(a+),K−	Fy(a+) Cx−
Affected child:	A	R_1R_2 (CDe/cDE)	MN.s	P−	Le(a−b−)	Lu(a+),K−	Fy(a−) Cx+
Father:	A_1	R_1r (CDe/cde)	MN.S	P+	Le(a−b+)	Lu(a+),K−	Fy(a+) Cx+
1st child:	A_1	R_2r (cDE/cde)	MN.S	P+	Le(a−b−)	Lu(a+),K−	Fy(a+) Cx−

All members of the family were tested with the maternal serum. The father and the affected child were positive, but the first child and, of course, the mother were negative. The maternal serum was titrated by various techniques with the father's cells. The results are shown in Table I.

TABLE I.—*Results of Titrating the Maternal Serum Against the Father's Cells*

Cells	Method				
	Saline Agglutination		Albumin Agglutination	Coombs Test	Papainized Cells
	20° C.	37° C.	37° C.	37° C.	37° C.
Father ..	Neg.	1:1	1:4	1:8	1:64

Investigations on Maternal Serum

The maternal serum was tested with a series of Group O cells known to contain the antigens C,D,E, c,d,e, C^w, C^u, M,N,S,s,P, Le^a, Le^b, Lu, K, Fy^a, Fy^b, Jk^a, Jk^b, Levay positive cells (Callender and Race, 1946), and Wright positive cells (Holman, 1953). Negative results were obtained, using all techniques. The serum was also similarly tested with:

11	samples of blood of genotype rr	(cde/cde)
23	" " " " "	R_1r (CDe/cde)
6	" " " " "	R_1R_2 (CDe/cDE)
7	" " " " "	R_2r (cDE/cde)
2	" " " " "	R_2R_2 (cDE/cDE)
3	" " " " "	R_0r (cDe/cde)

and with blood samples of genotype R′r (Cde/cde), R″r (cdE/cde), $R^{w}1r$ (C^wDe/cde), $R_y r$ (CdE/cde), $R^{u}1r$ (CD^ue/cde), $R^{u}2r$ (cD^uE/cde), and −D−/−D−.

The maternal serum was further tested with a total of 3,931 blood samples from healthy blood donors. These were selected only by reason of their ABO groups, and they comprised 1,727 Group A, 1,915 Group O, 210 Group B and 79 Group AB.

Initial testing of 267 samples was performed, using the tube albumin technique at 37° C., but the remainder of the tests were made with the papainized-cell technique in capillaries at 37° C. (Stratton, 1953). Control tests were used, each time employing a known positive reactor, and strong agglutination was obtained on each occasion. The Group O and A samples were tested with unabsorbed serum; the Group B and AB samples were tested with serum from which the anti-B agglutinins had been absorbed with papainized Group B Rh-positive cells. Four positive results were obtained when the 3,931 samples of blood were tested with the maternal serum; these were the 820th, 995th, 1,286th, and 1,779th samples tested. In each case the cell gave positive results with the maternal serum, using the albumin and Coombs techniques, as well as by the papainized-cell method. The four cell samples were tested further, with the following results:

Sample 1 (Lo):	A_2	R_1r	M.S	P+	Le(a+b−)	Lu(a−)	K− Fy(a+) Cx+
" 2 (Os):	O	R_1r	M.s	P+	Le(a−b+)	Lu(a−)	K− Fy(a−) Cx+
" 3 (Ho):	O	R_1R_2	MN.S	P+	Le(a−b+)	Lu(a−)	K− Fy(a−) Cx+
" 4 (Pri):	A_1	R_1r	M s	P−	Le(a+b−)	Lu(a−)	K− Fy(a−) Cx+

Each of these cell samples was shown to have a negative direct Coombs reaction. Tests on these samples and the father's cells with 20 fresh normal sera gave negative agglutination reactions in saline at 20° C. and 37° C.; polyagglutinability was thus excluded. The presence of the antigen A_1 was excluded in the case of the Group O propositi by testing them with the sera from Group O persons known to give strong reactions with A_1 cells. The father's cells and one of the propositi also gave a negative result when tested with anti-C^w, anti-Wright (Holman, 1953), anti-Miltenberger (Levine *et al.*, 1951), anti-Black, anti-Berrens (Davidsohn *et al.*, 1953), and anti-Graydon (Graydon, 1946) sera.

Investigation of Cell Samples Giving a Positive Result With the Maternal Serum

The father's cells and the four other cell samples described above were titrated with five anti-C typing sera in saline at 37° C. In Table II are shown the titres which were obtained by testing the sera with these cells, and with a number of cells containing the C agglutinogen, the latter giving negative results with the maternal serum of this case. It will be observed that several of the sera give much lower titres than they do with the control cells of genotype R_1r (CDe/cde) or R_1R_2 (CDe/cDE), although with one anti-C serum the results of testing the control cells and those giving a positive result with the maternal serum do not differ from one another. The detailed scoring of the titration of one of these anti-C sera with cells which gave positive results with the maternal serum, and with two control cells which did not, are shown in Table III. It will be seen that not only in certain cases are the titres lower, but the individual reactions between the various dilutions of the serum and the cells are weaker. Hence the titrations

TABLE II.—*Titration of Anti-C + Incomplete Anti-D Sera, Using Various Cells*

Cells	Rh Type	Result with Maternal Serum	Sera				
			Anti-C (i)	Anti-C (ii)	Anti-C (iii)	Anti-C (iv)	Anti-C (v)
Father	R_1r (CDe/cde)	+	1	1	16	2	4
Lo ..	R_1r (CDe/cde)	+	2	2	8	1	1
Pri ..	R_1r (CDe/cde)	+	2	2	16	4	2
Os ..	R_1r (CDe/cde)	+	4	2	16	4	4
Ho ..	R_1R_2 (CDe/cDE)	+	4	2	16	2	2
A ..	R_1r (CDe/cde)	−	64	8	8	32	16
B ..	R_1R_2 (CDe/cDE)	−	32	2	16	16	8
C ..	R_1R_1 (CDe/CDe)	−	32	8	16	32	16
D ..	rr (cde/cde)	−	—	—	—	—	—
E ..	R_2R_2 (cDE/cDE)	−	—	—	—	—	—

TABLE III.—*Results of Titration of Anti-C (i) with Normal Cells and Cells Positive with Maternal Serum*

Cells	Results with Maternal Serum	1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128	Control
R_1r (CDe/cde) ..	−	v	v	v	+++	+++	++	+	−	−
R_1R_1 (CDe/CDe)	−	v	v	v	+++	++	++	−	−	−
Father	+	+	−	−	−	−	−	−	−	−
Lo	+	++	+	−	−	−	−	−	−	−
Pri	+	+++	+++	−	−	−	−	−	−	−
Os	+	v	++	+	−	−	−	−	−	−
Ho	+	+++	++	+	−	−	−	−	−	−

with the control cells and with cells containing this special C antigen, as shown in Table III, have a characteristic pattern of reaction. Titration of anti-c showed that the father's cells contained only a single dose of c-agglutinogen.

Family Studies

The original family in which the case occurred has been studied as well as four other families. In these families it has been shown that the cells of members of the families which gave positive results with the maternal serum of the above case were all of type R_1r (CDe/cde), R_1R_2 (CDe/cDE), or R_1R_1 (CDe/CDe). Where the members of the families were of type R_1r or R_1R_2 the C antigen showed a similar modification to that described above, but in cases of type R_1R_1 the modification was masked by the presence of a normal C in the red cell. The family studies were consistent with this new Rh antigen (C^x) being inherited as a Mendelian dominant character.

Discussion

When this case first came to our notice it might not have received detailed consideration if it had not been for two factors. The first of these was the fact that the child was a severely affected case of haemolytic disease of the newborn and the diagnosis was not in doubt. The child's cells gave a strongly positive direct Coombs reaction when first examined on the 18th day. The second factor was that it is customary in this laboratory to make direct tests between the husband's cells and the maternal serum in those cases in which there is a suspicious history and in which no antibodies are found in the maternal serum by the usual methods of testing with standard cells. These include tests by saline and albumin agglutination techniques, by the Coombs technique, and using papainized red cells.

Following the direct tests between the husband's cells and the maternal serum the antibody was detected. It was obvious that this was an antibody of very unusual character, and consideration was given to the possibility of its reacting with a family antigen similar to others that had been described. This was thought to be especially likely when it was found that negative results were obtained with the usual test cells that were known to contain all blood-group antigens. The maternal antibody, nevertheless, was found to give strong positive results with the father's cells when these were treated with papain; the titre in this latter case was 1:64, whereas using the anti-globulin technique it was only 1:8. Several blood-group antibodies are known to give strong positive results with papainized red cells positive for the homologous antigen when they are prepared by the method of Stratton (1953). Since this was an ABO compatible pregnancy, and since Lewis and P antibodies are not known to be associated with haemolytic disease of the newborn, our attention was directed to the possibility of some antibody of the Rh series, or possibly a variety of anti-S or, on the other hand, some unknown antibody, which was responsible for this strong positive result when papainized cells were employed.

Tests for the rare Rh antibody, anti-C^w, proved to be negative, and when the maternal serum was tested with cells of type C^uDe/cde—a very uncommon type of cell (kindly provided by Dr. R. R. Race)—the results were also negative.

Our attention was further directed to the Rh antigen by the fact that when the father's cells were first typed they were routinely typed as R_0r (cDe/cde), and it was only on further examination, using several anti-C typing sera, that they were found to be of type R_1r (CDe/cde). It is not proposed to go into details in this paper concerning the reactions between these cells and various anti-C sera except to say that the cells appeared to have a modified C antigen which gave characteristic reactions. Cells which gave positive results with the maternal serum all gave this characteristic pattern of reaction except where this was masked by the presence of a normal C antigen, as in the genotype CDe/C^xDe. Had it not been for this characteristic pattern of reaction with various anti-C typing sera and the strong reaction which the maternal serum gave with papainized red cells we might not have thought the antibody to be one associated with the Rh blood group, but might have assumed it was reacting with a family antigen. This latter contingency was quite likely, since when testing random cell samples the first positive result was not obtained until 820 blood samples had been tested. These results suggested, therefore, that we were identifying an allele of Rh at the C-c locus. Moreover, family studies suggested that this was inherited as a Mendelian dominant character. That the serum of the mother was recognizing an allelic form of C could no longer be doubted when it was found with the peculiar form of C and the antigen recognized by the maternal serum showed absolute linkage in the family studies.

This antigen, which we proposed to call "C^x," appears to be analogous to C^w and to be a modification or mutation of C at the C-c locus. Unlike C^u, D^u, and E^u, but like C^w, it has an antibody which reacts with it specifically and characteristically. Anti-C^w antibodies occur in persons of genotype R_1r (CDe/cde), and similarly in this case a mother of genotype R_1R_2 (CDe/cDE) was immunized by a father of genotype C^xDe/cde. It is interesting to note that the difference between C^x and C is sufficient to cause immunization of the mother and the child to be affected with haemolytic disease of the newborn. Although this is the first C^x-positive living child that the mother has borne it is not necessarily the first antigenic stimulus, however, since the second pregnancy resulted in a stillbirth.

This case brings to our attention certain important factors. The first is that when a suspicious case of haemolytic disease of the newborn is observed, or where the clinical history suggests this diagnosis—for example, when there is a history of children affected with jaundice or anaemia or hydrops, or of multiple stillbirths—if no atypical maternal antibodies are found by routine methods then a direct test should be made between the father's cells and the mother's serum. The other interesting feature of this case is that the immunization of the mother might so readily have been thought to be due to a family antigen if the testing of a large number of random cell samples had not been undertaken. From our experience in this case it would seem that very large numbers of random tests need to be made before

one can conclude that an antigen is a true family antigen. Particularly is this so if there is the possibility of immunization to an antigen of the Rh series.

This antigen is very infrequent in the English population; it might be that in other populations the frequency would be greater.

Summary

A description is given of a case of haemolytic disease of the newborn due to a new Rh antibody, anti-C^x.

Anti-C^x antibody gives very few positive results when tested with random blood samples from the English population. Out of 3,931 random samples tested, four positive results were obtained.

The C^x antigen is considered to be an allele of Rh at the C-c locus. Its inheritance has been demonstrated.

The desirability of including direct tests between the husband's cells and the maternal serum in suspected cases of haemolytic disease, as well as the need for extensive investigations on antibodies thought to be reacting with family blood groups, is discussed.

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PORPHYRIN EXCRETION IN A PATIENT WITH DELAYED LIGHT-SENSITIVE PORPHYRIA

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Extensive knowledge based on modern techniques is becoming available on the porphyrin excretion in patients with acute porphyria (Nicholas and Rimington, 1953), but the present state of knowledge on the porphyrins of "delayed light-sensitive porphyria" is much less advanced. This term has been used (Prunty, 1952) in a suggested modified classification of porphyria to include cases referred to by previous authors as "porphyria cutanea tarda." The condition usually occurs in men of adult age and is not familial. Amongst the other changes, one important clinical manifestation is a bullous eruption of the skin produced by light and trauma. The present paper concerns additional data obtained from one of the rare cases of this condition seen by chance in this country.

Clinical Description of the Patient

A man aged 54, normally resident in South Africa, was admitted to St. Thomas's Hospital for investigation. He complained that he had had blisters on his hands for the past year. He has also suffered from arthralgia of the left hip, left knee, right ankle, and right shoulder for three years. There was no relevant family history. He had had blackwater fever in 1915, appendicectomy in 1924, and a cholecystectomy in 1945 for an illness accompanied by abdominal pain and jaundice. In 1952 radiological evidence of the presence of colonic diverticula had been obtained; at about this time he had had symptoms of diverticulitis. Apparently the porphyria became manifest a year before admission. Recurrent crops of blisters about 0.5 cm. in diameter occurred on the backs of his hands and fingers. They took four or five days to develop and then burst. They often contained a clear reddish fluid. This blistering did not appear to be related to exposure to sunlight. He had been treated with a sulphonamide for the diverticulitis without influencing the skin condition. There was some evidence that trauma to the skin favoured the production of these blisters. During the year his urine had been the colour of "dark ale," and had occasionally been dark during the last four years.

Physical examination showed a number of small circular scars on the backs of the hands and fingers, with a circular zone of slight pigmentation around some of them. When first seen three weeks before admission he had three blisters about 0.25 cm. in diameter on his hands, containing yellowish fluid, but these had disappeared by the time of his admission. There was a small rodent ulcer on the right cheek. The liver was enlarged one fingerbreadth below the costal margin, and scars from his two abdominal operations were present. There was a minor degree of osteoarthritis in the knees, hips, and right shoulder.

His urine on examination had a rosy hue and not the brownish-purple appearance of acute porphyria urine containing porphobilin. Porphobilinogen was never detected. On three consecutive days his pigment excretion measured:

Day	Urobilinogen mg./day	Total Porphyrin mg./day	Total Porphyrin Minus Uroporphyrin µg./day
1	9·4	2·4	37
2	6·6	4·8	80
3	3·0	4·4	126

The serum and cerebrospinal fluid contained no porphyrin. Faecal urobilinogen excretion was 295 mg. a day—a normal quantity. Serum total protein was 7.7 g. per 100 ml. (albumin 4.3 g. and globulin 3.4 g.). Thymol turbidity was 4 units; serum bilirubin 0.7 mg. per 100 ml.; cholesterol 159 mg. per 100 ml., of which 65% was esterified. The prothrombin time was 12 seconds (normal). The blood urea was 21 mg. per 100 ml., and endogenous creatine clearance 83 ml. a minute. The haemoglobin was 16.2 g. per 100 ml., and the packed cell volume 48%.

Urine Porphyrin

The porphyrin was isolated as previously described (McSwiney, Nicholas, and Prunty, 1950). Chromatography of the esters on columns of Al_2O_3 (Savory and Moore) and MgO Grade III (Nicholas, 1951) (see Diagram) to clean up the porphyrin gave a single main band (1), which on further chromatography on MgO Grade IV yielded a main band (1a) and traces of two other bands. This main fraction was crystallized, and the product had a melting-point at 211 to 213° C., and its α band at 624.3 mµ. Each band obtained from these three columns was submitted to paper chromatographic analysis, with the results shown in the Diagram. It should be noted that most of the urinary porphyrin was lost during preliminary purification.

There were two very faint bands, 1c and 1e, too little for any paper chromatography at all.

Fractionation of Urine Porphyrins

Urinary porphyrin. 24 mg. total from 6 litres of urine	Results of Paper Chromatographic Analyses		
	Method 1 (Nicholas and Rimington, 1949)	Method 2 (Falk and Benson, 1953)	Method 3 (Chu *et al.*, 1951)
Al_2O_3 Non-fluorescent → 1 mg.	1. Mainly 8*† + trace 6, 5, and 4		
MgO III Non-fluorescent → α625·0 mμ	1. Mainly 8* +some 6 and 7 and trace 4	Like Uro III, but Rf slightly greater	Strong spot between uro and copro I position
MgO IV → 1e, 1d, 1c, 1b → α624·3 mμ	1d. Mainly 4 and trace 3 1b. Mainly 6+7 and trace 8*		
1a → Crystallized m.p. 211–213° C.	1a. Mainly 8* and some 6 and 7	Like Uro III, but Rf slightly greater	Strong spot between uro and copro I position

* All octacarboxylic spots had relative fronts (Rf's) slightly greater than pure uroporphyrin; the appearance of these spots also was different, and the material cannot be regarded as typical uroporphyrin.

† The numerals indicate that porphyrins bearing this number —COOH groups in side-chains were found by the paper chromatographic method (cf. Nicholas and Rimington, 1949).

Faecal Porphyrin

This was extracted as ester (McSwiney *et al.*, 1950). Paper chromatography in the lutidine-water system (Nicholas and Rimington, 1949) of the crude ester extract showed only an atypical octacarboxylic porphyrin. Chromatography on MgO Grade III gave two small green-brown bands which were discarded and a main band (α band 620.8 mμ). This main fraction, derived from material which originally appeared to contain only octacarboxyl porphyrin, now on paper chromatography showed spots corresponding to a major component with either 6 or 7 carboxyl groups, together with traces of porphyrins with 3, 4, and 5 carboxyl groups. The evidence for degradation on the MgO column to substances with fewer –COOH groups was in this instance very clear. On paper chromatography after Chu, Green, and Chu (1951) there were three spots. The major component ran in the same position as pure coproporphyrin III, and there were two smaller amounts of material, one behaving like protoporphyrin, the other moving slightly slower than coprophyrin III.

Discussion

The case described was fairly typical, but in relative remission at the time of the examination. The most interesting feature was the apparent absence of light sensitivity, although blisters which almost certainly had contained porphyrin had clearly been present at times. The large urobilinogen excretion in the urine and slight enlargement of the liver suggested hepatic abnormality, and it may be that the attack of jaundice and abdominal pain for which cholecystectomy had been performed was related to the porphyria. The other features worth mention were the rosy colour of the urine, due to increased porphyrin excretion, and the absence of porphobilinogen. Both of these are important points of differentiation from the findings in acute porphyria, in which condition the brown colour is largely due to porphobilin.

Of special interest were the porphyrins found in the urine and faeces. It has been most usual to find uroporphyrin in the urine (Waldenström, 1937), apparently the isomeric uroporphyrins I and III being present together (Macgregor, Nicholas, and Rimington, 1952). These authors and Canivet and Rimington (1953) have together shown the presence of porphyrins with 2, 3, 4, 5, and 6 carboxyl groups, some of which have been more carefully characterized than others. Gray, Rimington, and Thomson (1948), however, in their case noted a remarkable instability of the ether-insoluble porphyrin fraction, and Macgregor *et al.* (1952) noted an unstable faecal porphyrin. This state of affairs was also apparent in the present case with regard to both urine and faecal porphyrins. The only stable porphyrin which could be isolated from the urine was a substance the ester of which had melting-point 211 to 213° C. and α band at 624.3 mμ. Apart from these two differences it also differed from uroporphyrin on paper chromatograms (see Diagram). It appears to be identical, by all three paper chromatographic methods employed, with the octacarboxylic porphyrin isolated by Canivet and Rimington (1953) for the first time from the pooled urine of five similar patients. Its similarity to the porphyrin of these authors extends to likeness of α band and melting-point. Neither of these porphyrins appears to be a known uroporphyrin.

The faeces of our patient yielded some protoporphyrin and coproporphyrin III, as might be expected. In addition there was plenty of evidence of decomposition of more highly carboxylated porphyrins, and it is impossible to state with any certainty what the original porphyrins were.

Summary

A brief case report of a man with "delayed light-sensitive porphyria" (porphyria cutanea tarda) is presented. The urine porphyrins were very unstable. The only porphyrin which could be isolated was an atypical octacarboxylic porphyrin like that of Canivet and Rimington (1953). The more highly carboxylated faecal porphyrins present underwent decomposition during processing, but an atypical octacarboxylic porphyrin was observed on paper chromatography of an early fraction.

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The 54th annual report of the Liverpool School of Tropical Medicine records that a number of cases of leprosy in persons resident in Britain came to light last year. "All these patients had been imported into this country actually with the disease, as a result of the repatriation of British subjects from India and of the immigration of individuals from various parts of the world following the disturbance in populations due to the recent war. Leprosy is a very chronic disease, which may not display itself for many years after its acquisition and which, when unsuspected, may escape diagnosis for years. In spite of the frequent importation of cases of the disease over many years, it does not spread here, and no case of infection acquired in this country has been seen at the school during the last 50 years. Thus the risk to our own population of the presence of such imported cases of the disease can be ignored as a public health problem. Contrary to popular belief, leprosy is the least infectious of all infectious diseases. The results of treatment with the recently introduced sulphone series of drugs have been most encouraging; but the treatment must be sustained under expert supervision over very long periods to prevent relapse."

THE NEUROMUSCULAR ACTIVITY OF SUCCINYLMONOCHOLINE IODIDE IN ANAESTHETIZED MAN

BY

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It was reported by Whittaker and Wijesundera (1952) that succinylcholine (succinyldicholine; SDC) is hydrolysed by horse serum cholinesterase in two steps: first one molecule of choline is split off at a fairly rapid rate from the SDC molecule and then the resulting succinylmonocholine (SMC) is hydrolysed more slowly to succinic acid and choline. Subsequently, Tsuji and Foldes (1953) and Lehmann and Silk (1953) have shown that SDC is hydrolysed in the same manner by human plasma and concentrated human plasma cholinesterase respectively. Foldes and Tsuji (1953) and Foldes (1953) also reported that SMC-I in doses of 2 to 2.5 mg. per kg. caused complete neuromuscular block for about 10 to 15 minutes and partial block for about 20 to 30 minutes in the sciatic-gastrocnemius preparations of cats anaesthetized with pentobarbitone. Lehmann and Silk (1953) found that in rabbits SMC (active cation) in doses of 2.5 mg. per kg. and 3.5 mg. per kg. produced paralysis without apnoea for 150 and 550 seconds respectively. Doses higher than 5 mg. per kg. regularly caused respiratory paralysis in rabbits. Ellis *et al.* (1953) investigated the neuromuscular effects of SMC-I in several species and found that on a molar basis its activity varied from 1/24 to 1/62 of that of SDC-Cl_2. They also found that in mice SMC-I is 1/14 as toxic as SDC-Cl_2.

Present Investigation

In view of the fact that SDC-Cl_2 is being used with increasing frequency for the production of muscular relaxation for operative procedures, and that occasionally as much as 12 mg./min. of SDC-Cl_2 has been administered to patients for prolonged periods (Bourne *et al.*, 1952), it seemed worth while to investigate the muscle-relaxant properties of SMC-I in humans to find out whether or not the SMC concentrations resulting from the hydrolysis of the relatively large quantities of SDC-Cl_2 administered to patients in the course of long operative procedures might have any effect on neuromuscular conduction. Since it is not possible to predict from the effects of muscle relaxants observed in one species the effects to be expected on another species (Paton and Zaimis, 1950; Unna *et al.*, 1950) such information could be obtained only by observing the effect of the administration of SMC-I on human volunteers or on patients requiring muscular relaxation for various operative procedures. We chose the latter course.

At first SMC-I was administered in doses of 1 mg. per kg. to patients anaesthetized with combinations of thiopentone sodium/N_2O–O_2/pethidine according to a previously described technique (Foldes *et al.*, 1952). This dose of SMC-I had no discernible neuromuscular effect. Therefore the initial dose of SMC-I was gradually increased in subsequent patients to 5 to 7 mg. per kg. body weight. With this dosage, muscular relaxation developed in three to five minutes and lasted from eight to twelve minutes. This relaxation could be maintained by the repeated intravenous injections of 3 to 4 mg. per kg. of SMC-I at intervals of eight to twelve minutes. The resulting muscular relaxation was adequate for the performance of various intra-abdominal operations. The respiratory depth of the patients was hardly affected at times when good abdominal relaxation was present. It has been the impression of the anaesthetists and surgeons that increased diaphragmatic activity compensated for the intercostal paralysis in the maintenance of adequate respiratory depth.

The jaw musculature and the vocal cords were not as well relaxed even after 7 mg. per kg. as after the use of some other neuromuscular blocking agents, but the patients could be intubated without major difficulty.

It was observed that SMC-I markedly potentiated the neuromuscular blocking activity of subsequent doses of SDC-Cl_2 at a time when the patients had apparently recovered from the effects of the former. In a 22-year-old woman weighing 75 kg. the injection of 20 mg. of SDC-Cl_2 produced in 40 seconds slight respiratory depression for 225 seconds. Seven minutes after the intravenous administration of 350 mg. of SMC-I, an identical 20-mg. dose of SDC-Cl_2 produced in 25 seconds respiratory arrest for 270 seconds, and some respiratory depression for an additional 210 seconds.

Owing to the limited supply of SMC-I at our disposal, it was used for the production of muscular relaxation in only 10 patients. The operative procedures included 3 appendectomies, 4 cholecystectomies, 2 hysterectomies, and 1 exploratory laparotomy. Satisfactory abdominal relaxation was obtained in all patients without the development of respiratory arrest or more than a moderate degree of respiratory depression. The pulse and blood pressure of the patients remained remarkably constant. The muscular relaxation had a tendency to wear off abruptly unless a fractional dose was administered at the first sign of its fading effect. In general, the relaxation obtained with SMC-I resembled that obtained with decamethonium.

No prolonged post-operative respiratory depression was observed in any patient in this small series. Respirations became normal within 8 to 12 minutes after the administration of the last fractional dose in all instances.

Muscular twitchings occasionally seen with decamethonium and more frequently with SDC-Cl_2 were not observed with the use of SMC-I.

The urinary excretion of SMC-I was followed in two patients. Urine was collected during and 15 minutes after the administration of a relaxant dose of SMC-I. The patients excreted 11.8% and 14.5% of the administered SMC-I during this period. In contrast to this less than an average of 3% of the administered SDC-Cl_2 could be recovered from patients under identical circumstances (Foldes and Norton, to be published).

Discussion

The neuromuscular effect of SMC-I represents a transition between that of decamethonium and SDC-Cl_2. The onset and duration of the neuromuscular blockade with SMC-I resembles that seen with the use of decamethonium. On the other hand, its elimination from the body is similar to that of SDC-Cl_2. Whereas decamethonium can be recovered almost quantitatively unchanged in the urine after its administration (Paton and Zaimis, 1952), most of the SMC-I is hydrolysed in the body to succinic acid and choline. However, since the hydrolysis of SMC-I by the plasma cholinesterase is much slower than that of SDC-Cl_2, urinary excretion plays a greater part in the elimination of SMC-I than is the case with SDC-Cl_2.

The findings presented indicate that in the average patient 0.3 to 0.4 mg./kg./min. of SMC-I gave adequate muscular relaxation without the development of undue respiratory depression. It has been our experience that the administration of 0.05 to 0.15 mg./kg./min. of SDC-Cl_2 was necessary in a large group of patients for the production of good

muscular relaxation. Since the ratio of the molecular weights of SMC-I and SDC-Cl_2 is about 0.8, the hydrolysis of 0.05 to 0.15 mg. of SDC-Cl_2 will produce the equivalent of 0.04 to 0.12 mg. of SMC-I. This dose of SMC-I has little or no effect on neuromuscular conduction in patients whose ability to hydrolyse and excrete SMC-I is unimpaired. However, in patients with low cholinesterase activity, especially if their kidney function is also diminished, the administration of relatively large doses of SDC-Cl_2 for prolonged periods might lead to the accumulation of SMC in sufficiently high concentrations to potentiate the neuromuscular action of the unhydrolysed SDC-Cl_2. Such a set of circumstances can arise if muscular relaxation is maintained in patients with low plasma cholinesterase activity with SDC-Cl_2 by the "apnoeic technique."

With this technique the administration of SDC-Cl_2 is carried to a point where the patient's voluntary respiratory movements are completely abolished and gas exchange is maintained by manual compression of the breathing-bag of the anaesthesia machine. Since the administration of SDC-Cl_2 in amounts many times higher than the apnoeic dose has no discernible effect on blood pressure, pulse rate, or any other physiological process, there is no sign that would indicate whether just enough SDC-Cl_2 is administered for production of apnoea or whether large doses of SDC-Cl_2 accumulate in the organism. If the latter of the two possibilities occurs in patients with low plasma cholinesterase activity and with decreased urinary excretion, prolonged post-operative respiratory depression will result. Since adequate muscular relaxation can be obtained with SDC by utilizing the difference in sensitivity to this agent between the diaphragm and intercostals, there seldom is a need for the application of the apnoeic technique.

It is unlikely that SMC plays a similar part in the prolonged respiratory depression occasionally observed after the administration of a single large dose of SDC-Cl_2 (Hewer, 1952; Love, 1952; Harper, 1952; and others). The hydrolysis of as large a dose as 100 mg. of SDC-Cl_2 will yield only about the equivalent of 80 mg. of SMC-I, and this dose is not likely to have any neuromuscular blocking effect. The prolonged apnoea under such circumstances is caused either by an exceptionally low plasma cholinesterase activity of the patient or by the combination of acapnia due to too energetic controlled respiration, and reflex breath-holding arising from the stimulating effect of the endotracheal tube on the larynx and trachea in the patient in whom the level of general anaesthesia was allowed to become too light.

Owing to the relatively large doses in which SMC-I has to be administered, the less satisfactory relaxation obtained, and the lack of rapid and easy controllability of its neuromuscular effect, SMC-I does not seem to offer any advantages in comparison with other available muscle relaxants, especially SDC-Cl_2.

Summary

In man SMC-I in doses of 5–7 mg. per kg. produced in three to five minutes muscular relaxation of 8 to 12 minutes' duration.

Muscular relaxation could be maintained by repeated intravenous injections of SMC-I in doses of 3–5 mg. per kg. 8 to 12 minutes apart.

These doses of SMC-I caused little respiratory depression.

The administration of SMC-I markedly potentiated the neuromuscular action of subsequent doses of SDC-Cl_2.

The possible role of the accumulation of SMC in the development of prolonged apnoea after the use of SDC-Cl_2 is discussed.

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BACTERIAL ENDOCARDITIS DUE TO CHROMOBACTERIUM PRODIGIOSUM

REPORT OF A CASE

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Chromobacterium prodigiosum (*Serratia marcescens*) is usually regarded as non-pathogenic for man, and Wilson and Miles (1946) were unable to quote any indubitable report to the contrary. In 1952, however, Patterson, Banister, and Knight described a case of septicaemia due to this organism, and reviewed the literature concerning human infections with members of the *Chromobacterium* group. They quoted 21 records of infection by *Chr. prodigiosum*, including their own, only one of which was a case of endocarditis (Wheat, Zuckerman, and Rantz, 1951).

Case Report

An African man aged 38 was admitted to the Gold Coast Hospital, Accra, on April 30, 1953, after a month's sickness; this began with fever and headaches, accompanied by rigors. After taking mepacrine and "phensic" tablets he was able to continue his work as an omnibus inspector. About a week before admission he had had further headaches with fever and pain in the neck. He attended the out-patient department on April 25, when a blood film proved negative for malarial parasites, but the urine was found to contain albumin. He was given an injection of sulphasolucine, 5 ml., and another of quinine, 10 gr. (0.65 g.), both intramuscularly, as well as 2 ml. of mersalyl. He was subsequently referred to A. J. H. and was admitted for investigation.

On admission he complained of feverishness and pain in the umbilical region. His temperature was 101° F. (38.3° C.). A blood film was again negative for malarial parasites and there was a heavy cloud of albumin in the urine. He was systematically examined on May 1. It was noticed that he had lost weight. He was obviously a sick man, but in no way distressed. No rash was found on his skin and his temperature was 104.2° F. (40.1° C.). His bowels had been open daily and the stools were semi-solid. His tongue was moist and a little furred. Except for the complaint of pain in the umbilical region no abnormality was found in the alimentary system. The chest was clear and the sinuses appeared to be normal; the respiration rate was 30 a minute. The cardiovascular system showed nothing abnormal beyond a pulse of 120 a minute. The patient complained of a frontal headache, which was worse when the fever was high in the evenings, but a clinical examination

of the central nervous system proved negative. There was no lymphadenitis. The urine was passed freely without pain.

A white blood cell count showed a total of 11,200 leucocytes (70% polymorphs, 25% lymphocytes, 2% eosinophils, 2% monocytes, 1% basophils). Coliform bacteria were cultured from the urine, and were at the time reported as *Bact. coli*, a finding which was later doubted. Serological reactions with *Salmonella* antigens were negative. A Weil–Felix test gave the following result: *Proteus* OX_2 1/160, X_K 1/40 X_{19} 1/80. Two successive stool cultures on May 6 and 8 proved negative. Blood culture on May 2 was discarded as sterile 21 days later.

On May 6 treatment was begun with alkalis and "sulphatriad" in full doses. After three days, since there was no response, he was given chloramphenicol, 2 g., as a loading dose and 1 g. every four hours thereafter; after four days, when he had received 25 g., the available supply of chloramphenicol was exhausted, and although there had been a favourable response this was not maintained when the drug was stopped. By this time blood had appeared in the urine. The patient's condition had deteriorated, and he was very weak; he was thought to be too ill for cystoscopy or pyelography, both of which had been considered. Streptomycin was given from May 16 in doses of 1 g. daily, but with no beneficial effect.

On May 20 a further blood culture was taken, by which date the only positive finding had been the growth of coliform bacteria from the urine. On May 11 a re-examination revealed a full appearance of the abdomen; because of general resistance palpation was difficult, but the liver, spleen, and kidneys could not be felt. Rectal examination revealed generalized tenderness only. The lungs remained free from clinical signs, but an apical systolic cardiac murmur was noted; the significance of the latter finding was overlooked. The urine continued to show a heavy albuminuria with red and white blood cells. On May 25 a third blood culture was taken which five days later yielded a pure growth of *Chr. prodigiosum*, which was reported as being probably a contaminant. The patient's condition continued to deteriorate, and he died on June 2 without a diagnosis having been made.

Post-mortem Examination

A post-mortem examination was made 19 hours after death by Dr. F. C. Harris. The main finding was a friable vegetation, buff in colour, attached to the free margin of the posterior cusp of the mitral valve; there was some erosion of the cusp. A haemorrhagic nodule, 0.5 cm. in diameter, was found on section of the liver. There were five recent infarcts in the spleen, which was moderately enlarged, and a large white infarct involving the whole of the upper pole of the right kidney.

On the following day the blood cultured on May 20 was found to have produced a belated pure growth of *Chr. prodigiosum*, after 15 days' incubation in a combined liquid and solid medium put up in the same bottle by a technique modified by Hughes (1953) from that described by Castaneda (1947); the important feature of this technique is that it prevents contamination of the culture between the inoculation of the medium and the isolation of the organism, and it is thus quite certain that the growth of *Chr. prodigiosum* in a second blood culture could not have been due to laboratory contamination. The cut surface of the mitral vegetation removed at necropsy was rubbed on the surface of a blood-agar plate, and this also yielded a pure culture of *Chr. prodigiosum*. Thus *Chr. prodigiosum* was isolated from two ante-mortem blood cultures taken on different dates, and also from the mitral vegetation after death.

Bacteriology

The culture of *Chr. prodigiosum* isolated from this case had the following characteristics: Motile Gram-negative cocco-bacillus without a capsule. Good growth on nutrient agar, sheep's blood agar, MacConkey agar, and "bacto" SS agar. Growth at room temperature (about 25° C.) was slightly better than at 37° C. No haemolysis on blood agar. On nutrient agar the colonies after 24 hours were from 0.5 to 1 mm. in diameter, smooth, shiny, and low convex with entire edge, and bright red in colour. After 48 hours the confluent growth was orange-red, and the single colonies were between 1 and 2 mm. in diameter, umbonate, surface becoming granular, with pink centre and orange-red periphery. After five days the colonies were from 3 to 4 mm. in diameter with a rough appearance.

The pigment was very slightly soluble in water, moderately soluble in absolute alcohol, and completely removed from a peptone water culture by chloroform. In peptone water and in gelatin a red surface ring was formed, but this did not occur in broth or in glucose phosphate medium. The colonies on MacConkey agar were bright red; this appearance, coupled with a red colour in lactose-peptone water simulating that of acidified Andrade's indicator, probably resulted in an erroneous report of *Bact. coli* in the patient's urine, although if *Chr. prodigiosum* had been recognized at that time it is improbable that the finding would have been regarded as significant.

In peptone water "sugar" media, acid and a moderate amount of gas were formed from dextrose, saccharose, maltose, mannitol, and salicin; there was no fermentation of lactose, dulcitol, arabinose, rhamnose, xylose, and inositol. There was no growth in Koser's citrate. Indole was not formed. H_2S was formed on liver infusion agar, but not in peptone water, when tested for by a lead acetate strip in the top of the tube. Catalase was not formed. The methyl red test was negative. In a five-day glucose phosphate culture the Voges–Proskauer test was negative by O'Meara's method but positive by Barritt's modification of the test. Coagulated serum and gelatin were both liquefied.

In vitro sensitivity tests showed the strain to be completely resistant to penicillin and aureomycin, but sensitive to chloramphenicol and streptomycin. White mice died within 12 hours when injected intraperitoneally with 0.5 ml. of a 24-hour broth culture; these mice showed pleural exudates.

The specific identity of the organism described by us as *Chr. prodigiosum* may be open to doubt. Breed, Murray, and Hitchens (1948) used the formation of gas in carbohydrate media as a criterion for the separation of species within the genus *Serratia*, and on this ground our organism could not be *Chr. prodigiosum*. Wilson and Miles (1946), however, stated that some strains of *Chr. prodigiosum* do form gas. Again, Breed *et al.* used acetyl-methyl-carbinol formation as a means of separating species, but without specifying what method they used for testing for this metabolite; the results with our strain were equivocal by this standard also, and it was not possible to classify it according to the criteria of *Bergey's Manual*. Without aspiring to taxonomic authority we have therefore thought fit to call our organism *Chr. prodigiosum*, a course in which we are fortified by the treatment of this group of organisms by Wilson and Miles.

It is of interest to note that both in our own case and in that described by Patterson *et al.* (1952) there was some clinical response to chloramphenicol, although in both cases the treatment with this drug was interrupted by extraneous circumstances. Patterson *et al.* also found that their strain was highly sensitive to neomycin, and one of these two antibiotics would appear to be the treatment of choice in cases of infection by this organism.

Summary

A case of acute endocarditis is described in which *Chr. prodigiosum* was isolated twice from the blood during life and again from an endocardial vegetation after death. The strain was sensitive *in vitro* to streptomycin and chloramphenicol, and slight improvement followed treatment with the latter drug. The characteristics of the organism are described. Chloramphenicol, or perhaps neomycin, may be the

treatment of choice should further cases of this rare infection by a common saprophyte be brought to light.

Our thanks are due to Dr. F. C. Harris for permission to make use of his necropsy report, and to Dr. L. G. Eddey, Chief Medical Officer, for permission to publish this paper.

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Medical Memorandum

Congenital Tuberculosis after Pleural Effusion in the Mother

A woman aged 23 was admitted to a general hospital with a left pleural effusion on December 1, 1949, when five months pregnant. There was no family history of tuberculosis or known contact. She did not remember having had any illness until July, 1949, when her husband was at home on leave and she had a cold and lost weight. In the early weeks of her pregnancy she gained weight, but began to get pains in the left chest in October. The findings on aspiration of approximately 500 ml. of straw-coloured fluid were: red cells, moderate numbers; lymphocytes, fairly numerous; polymorphs, nil. The blood picture was: haemoglobin, 64%; leucocytes, 8,000 (polymorphs 66%, lymphocytes 30%, monocytes 3%, eosinophils 1%). There was nothing abnormal on urinary examination. On January 7, 1950, after the illness had run a typical course, she was discharged home, apyrexial, to await admission to a sanatorium.

On February 7, when admitted to a chest hospital, she was symptomless. The physical signs were those of a small pleural effusion, the anaemia persisted, and the sedimentation rate was 18 mm. (Westergren). Radiologically an opacity remained in the left lower zone. Treatment was by rest and haematinics whilst the pregnancy proceeded uneventfully to full term.

On April 17 she complained of generalized aches and pains and there was an evening pyrexia to 99.2° F. (37.3° C.). Next day the symptoms were improved, and on the 19th she went into labour and was delivered of a normal female child the same day, after transfer to the maternity hospital. The child was isolated. The placenta was examined and recorded as "complete." During the puerperium she had an evening pyrexia of 101° F. (38.3° C.) and was readmitted to the chest hospital on April 25, when treatment was begun with streptomycin, 1 g. daily, and 18 g. of para-aminosalicylic acid. On April 27 the baby died, aged 8 days.

FINDINGS AT NECROPSY ON THE BABY

The body was well nourished and of normal colour. About 5 ml. of clear yellow fluid was present in both pleural cavities, and a little less than 5 ml. in the peritoneal cavity. Both lungs showed severe congestion and oedema. Weight, right 62 g., left 58 g. Dispersed throughout the lung substance of both sides and beneath the pleural surfaces were miliary tubercles consisting of grey-yellow areas 2–3 mm. in diameter and some the size of a small pinhead. The tubercles were either one size or the other, there being none of intermediate size.

The heart showed no congenital or acquired abnormality. The peritoneal cavity contained about 10 ml. of free fluid. There was matting together of the structures around the spleen and yellowish-white exudates were present in small amount. The spleen weighed 35 g. and measured 7.5 by 4 by 3 cm. It was engorged and contained tubercles similar in size to those in the lungs. A direct smear from the cut surface revealed many tubercle bacilli. The liver weighed 260 g., and contained tubercles throughout, and beneath its peritoneal surface. The most interesting feature of this organ was the presence of a mass of glands in the hilum. These measured 3 by 2.5 by 2 cm. The cut surface was yellow and caseous-looking. The kidneys, bladder, uterus, and alimentary tract appeared to be normal. The brain was not congested and seemed normal in every respect, no evidence of tubercle being present.

PROGRESS OF MOTHER

The woman continued to have an evening pyrexia until June 15, by which date 50 g. of streptomycin had been given. Apart from the pyrexia the post-puerperal period continued normally, but the reappearance of menstruation was delayed until August 12. No abnormal physical signs were present in the chest, and radiography demonstrated only a clearing of the pleural opacity. Clinical improvement with a gain in weight began with the subsidence of the pyrexia, but chemotherapy was continued until August 28, when 120 g. of streptomycin had been given. At this time no clinical or radiological abnormality could be detected. She was discharged home on October 19, apparently a healthy woman, the sedimentation rate being 4 mm. (Westergren) and her weight 128 lb. (58 kg.).

Subsequent progress during 1950 was uneventful and her weight increased to 143 lb. (64.8 kg.). On February 26, 1951, a laparotomy was performed and section of the Fallopian tubes and appendicectomy were carried out. No abnormality of the pelvic organs was detected. Progress was again uneventful until December, 1951, when a fluctuant swelling was detected in the left breast. At incision in February a localized abscess was removed.

Microscopically, non-specific chronic inflammation was reported and culture of the material evacuated remained sterile, but a sinus persists, although the patient remains well three and a half years after the birth of her child.

COMMENT

The primary lesion in the hepatic glands of the infant is consistent with haematogenous infection via the placenta, whilst its size and maturity would suggest that it originated a considerable time before birth, probably coincident with the onset of pleurisy in the mother. The miliary tuberculosis in the lungs, spleen, and liver would seem to be a secondary haematogenous dissemination in which the mother shared infection just before delivery, the usual effects of such dissemination being suppressed by streptomycin.

Any typical primary focus other than the pleural effusion in the mother remains undisclosed, but it has been shown (Kayne *et al.*, 1948) that quite a large proportion of "idiopathic" pleural effusions occur in close time relationship with the primary infection.

This case contrasts with the almost invariable sequel of healthy infants born to mothers suffering from progressive, advanced, or miliary tuberculosis.

I am informed by Mr. L. E. Perkins that in veterinary practice congenital tuberculosis was not so uncommon and was found in association with primary tuberculous infection, usually believed to be in the uterus, rather than in association with established or widely disseminated tuberculosis.

CONCLUSIONS

Treatment by chemotherapy is justified in primary tuberculosis occurring in pregnancy. Routine B.C.G. vaccination at birth of babies born to such tuberculous mothers should be preceded by a Mantoux test.

I am indebted to Dr. J. F. Horley for the necropsy findings.

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Reviews

PITUITARY CHROMOPHOBE ADENOMAS

Pituitary Chromophobe Adenomas: Neurology, Metabolism, Therapy. By Professor John I. Nurnberger, M.D., and Saul R. Korey, M.D. (Pp. 282; illustrated. 55s.) New York: Springer Publishing Company Inc. London: Lange, Maxwell and Springer. 1953.

On the first page of the introduction the authors rather shock the conventional by suggesting that the original case of Fröhlich, always thought to be due to craniopharyngioma, and the painful adiposity case of Dercum and McCarthy, 1902, were both probably due to chromophobe adenomas, presumably with involvement of the adjacent hypothalamus. This conclusion may be questioned. In the first chapter the authors consider the anatomy of the pituitary and the detailed main paths of the secretion of the anterior pituitary gland directly entering venous channels. They also discuss the influence of the hypothalamus on the anterior pituitary gland and evidence of mediation by humoral means, such as by hypothalamic hormones or metabolites, being conveyed by the blood stream to the anterior pituitary gland. Diagrams showing the amazing variation in the shape of the sella turcica in normal individuals are of value, as it is not infrequent to meet queries, or wrong interpretations, about sella turcicas that do not conform to the usual shape.

Metabolism is discussed along modern lines but with attention to historical landmarks. The authors indicate that a low level of activity of the thyroid gland and of the adrenal cortex persists after complete hypophysectomy. Inactivation of thyrotrophic hormone by the thyroid gland may explain why this hormone may not be found in the blood in thyrotoxicosis by methods that detect an excess in myxoedema. The contrasting effects of pituitary growth hormone and adrenal glucocorticoids on protein metabolism are well brought out, but in considering the mechanisms by which the anterior pituitary causes nitrogen retention the authors mention the production of gonadal testosterone without making clear the importance of adrenal androgens, a contribution which is noteworthy physiologically and pathologically.

The authors give an adequate account of the neurological signs and complications and the metabolic defects that follow destruction of the anterior pituitary gland. Optic atrophy and bilateral hemianopia were frequent, but papilloedema occurred in 7% due to involvement of the third ventricle or to venous compression. Third-nerve involvement was more frequent than fourth or sixth. Large tumours produced a variety of neurological features. Haemorrhage into a cystic tumour was the cause of rapid onset of neurological signs. Detection of hypothalamic compression was made by encephalography, showing distortion of the floor of the third ventricle, and was found to be present in as high as 88% of cases, although in 30% of these there were no referable symptoms. Eighteen of the 68 patients with hypothalamic involvement showed agitation, attacks of drenching perspiration, and occasional hypothermia. A similar number suffered from lethargy, emotional depression, and excessive somnolence. Epileptic phenomena associated with drenching perspiration and peripheral vasodilatation was observed in 6 of the 68 patients with hypothalamic involvement. Obesity with polyphagia occurred only in six.

None of the cases of chromophobe adenoma showed any pigmentation, and this is recorded as being true of another 100 patients observed by German. In contrast with this was the presence of pigmentation in 25% or more of patients with Simmonds's disease and, according to Davidoff, in one-half of the acromegalics. The contrast between patients with chromophobe adenoma and with Simmonds's disease is attributed by the authors to the fact that in Simmonds's disease the posterior pituitary usually remains intact. Apart from this, it should be pointed out that occurrence of pigmentation with Cushing's syndrome and with A.C.T.H. or cortisone therapy has complicated our conception of its origin as a deficiency manifestation. A.C.T.H., or an associated substance, seems to be an important factor in explaining the difference between the frequency of pigmentation in Addison's disease and its relative rarity and mildness in Simmonds's disease.

The chapter on radiography indicates how a chromophobe adenoma may enlarge and invade in all directions, and the frequency and extent of invasion and distortion of the third ventricle and hypothalamus, as shown by pneumo-encephalography, comes as a surprise to the endocrinologist (reviewer). Further information on the radiographic differentiation of craniopharyngioma (for example, the frequency of calcification, particularly in children) would be welcome in a subsequent edition of this book.

The section on pathology is a little disappointing, but this may be innate in the problem. Malignant changes are rare, but cystic degeneration and haemorrhage not infrequent. 10% of the tumours showed transitional eosinophil cells, and clinical evidence of mild acromegaly was traced. Transitional basophil cells are recorded as being very rare. It should also be recognized that a typical Cushing syndrome has been recorded, paradoxically and rarely, with a chromophobe pituitary tumour. In most cases in this present study there was no clue to the origin or cause of the chromophobe adenoma. However, the authors draw attention to the fact that oestrogens can cause chromophobe adenoma in rats, and that this may be associated with dwarfism, atrophy of thyroid and gonads, but enlargement of the adrenal cortex. The latter circumstance would hardly support their hypothesis that the pathogenesis of chromophobe adenoma in man is similar. Surgery, radiography, and medical substitution therapy are also ably discussed.

This book is a very valuable and brief summary of present-day knowledge of pituitary chromophobe adenomas, to which knowledge the authors have made careful and important contributions.

S. LEONARD SIMPSON.

HYPERTENSIVE DISEASES

Hypertensive Diseases: Cause and Control. By Henry A. Schroeder, M.D., F.A.C.P. (Pp. 610; 164 illustrations and 3 coloured plates. 75s) London: Henry Kimpton. 1953.

The author of this book and his colleagues at St. Louis have been studying hypertension for a number of years, and the book contains a vast amount of knowledge derived from their own work and that of others. The index of authors contains some 900 names. The book deals exhaustively with the pathology of hypertension, its biochemistry, diagnosis, and treatment; but, as is not unusual in American books, less attention is paid to natural history and morbid anatomy. Nevertheless there is a case report of what must be one of the longest periods of observation of a patient with hypertension yet recorded. This concerns a woman who was found to have a systolic pressure varying from 160 upwards at age 26 and who was followed till her death from a heart attack at age 67.

Dr. Schroeder does not attempt any final definition of hypertension and hypertensive cardiovascular disease beyond the fact of raised blood pressure, but he devotes a good deal of attention to certain special aspects and clinical types. These are nephrogenic, neurogenic, and endocrine hypertension. He does not think that much can be expected from dietetic treatment except in endocrine disturbances, and, though he gives a fair description of sympathectomy and subtotal adrenalectomy, he quotes with approval the fifth of Loeb's rules of therapeutics—"Keep the patient out of the hands of the surgeon." The numerous drugs used in treatment of hypertension, many of them introduced in the last few years, are fully considered. Finally, Dr. Schroeder lays down a schedule for investigation of patients with hypertension and for their treatment with a combination of 1-hydrazinophthalazine ("apresoline") and hexamethonium by mouth. Apresoline is believed to neutralize the hypertensive factors which are derived from the ischaemic kidney. This is therefore a two-pronged attack on the nephrogenic and neurogenic factors in hypertension. Few cases have been treated for longer than two years and it is therefore too early to appraise the results, but striking improvement has been observed in malignant hypertension. The book is well produced, indeed perhaps too expensively for what is essentially a progress report. Nevertheless it is a mine of information about this common disease.

L. J. WITTS.

TUMOURS OF BONE

Tumors of Bone: A Roentgenographic Atlas. Annals of Roentgenology, Volume XXI. By Bradley L. Coley, M.D., F.A.C.S., and Norman L. Higinbotham, M.D., C.M., F.A.C.S. (Pp. 216; 172 figures. 75s.) London: Cassell and Co. Ltd. 1953.

That the present atlas of radiology has been written by two orthopaedic surgeons, and is being reviewed for these columns by a pathologist, indicates the extent of overlap of interests in the field of diagnosis of bone tumours. This overlap is, in fact, a most desirable thing, and one of the great assets of the present volume, which comes from the Bone Tumour Service of the Memorial Centre for Cancer and Allied Diseases in New York, is the almost equal familiarity with the clinical presentation and behaviour, the radiological appearance, and the pathology of tumours of bone that its authors possess.

Within the confines of a brief atlas it is not possible to present scientifically all the data in each of these fields on the cases selected for illustration. Radiographs have pride of place—as, in a radiographic atlas, they should—though there is usually a brief clinical note with each *x*-ray picture and occasionally a photograph of the pathological specimen from the case or an appropriate photomicrograph placed beside it.

With few exceptions biopsy examination has been carried out in the cases chosen for illustration, and the radiological diagnosis thus substantiated or modified. While the reader has to take the authors' word for the authenticity of the biopsy reports, he has the feeling that his confidence in them is rarely misplaced. The general classification of the various conditions discussed, and views on the extent of their practical separation from each other, are in keeping with present-day trends in pathology. Among the benign tumours of bone, for example, the conditions discussed and illustrated include "osteoid osteoma," "nonosteogenic fibroma," and "benign chondroblastoma," although it is surprising to find no mention of "chondromyxoid fibroma."

A subject to which repeated reference is made, and one where the authors give an accurate and balanced account, concerns the degree of correlation to be expected between radiological and biopsy diagnosis in the field of bone tumours. With cartilaginous tumours, in particular, when a biopsy diagnosis of "chondroma" is suggested, just emphasis is given to the importance of radiological evidence of possible malignancy in areas of the tumour outside the region of biopsy. Indeed, the authors' general principle should be as acceptable to the pathologist as to the clinician that "where the *x*-ray film and the clinical setting suggest a malignant tumor and a study of microscopic sections does not corroborate this impression, one must be extremely hesitant about accepting the pathologist's report as the final word." Both radiological and histological diagnosis have their limitations, and the clinician dealing with bone tumours should be aware of them in some detail.

The standard of illustration of the book is good; it is well arranged and well indexed. In short, it is a volume which can be depended on to make its mark as a reliable account of the radiological characteristics of each of the very numerous "entities" with which we are concerned in the diagnosis of tumours of bone.

H. A. SISSONS.

EMOTIONS AND PELVIC SYMPTOMS

Psychosomatic Approach to Gynecology and Obstetrics. By Fritz Wengraf, M.D. American Lecture Series. (Pp. 346. 50s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1953.

The author of this monograph sets out to emphasize the need to recognize the emotional factor in the aetiology of pelvic disease and symptoms if they are to be properly understood and treated. It is clearly intended mainly for general practitioners and for those who specialize in obstetrics and gynaecology, so that abstruse terms are avoided so far as possible, and the main body of the book is introduced by general psychiatric considerations, with definitions of states such as anxiety and hysteria and explanations of concepts such as conversion and organ language.

In the two sections dealing respectively with gynaecological and obstetrical conditions are to be found the expected favourites such as dysmenorrhoea, amenorrhoea, functional uterine haemorrhage, frigidity, menopausal symptoms, menstrual tension, nausea, and vomiting of pregnancy, and the effect of the emotions on pregnancy, labour, and lactation, and vice versa. There are also others less expected such as leucorrhoea, abortion, and pica in pregnancy, and a helpful section on a woman's mental reactions before and after a gynaecological operation. As is usual in books of this kind, illustrative cases are quoted in detail.

It is all very readable and, if anything, errs on the side of making the subject appear too easy—glib conjectures sometimes masquerading in the guise of explanations of abstruse problems. However, in the section on treatment the author makes a real attempt to guide the general practitioner in the handling of the difficult class of patient concerned. Whether it all be accepted or not, it is an interesting book, and it presents an aspect of obstetrics and gynaecology which the good doctor cannot overlook.

T. N. A. JEFFCOATE.

GUIDE TO PHYSIOTHERAPY

The General Practitioner's Guide to Physiotherapy. By Janet Dennison, M.C.S.P. (Pp. 39. 6s.) London: William Heinemann. 1953.

This little book is agreeably written and contains much good sense. The author comments on the wide scope of physiotherapy and the popularity of these forms of treatment in present-day medicine. The history of the Chartered Society of Physiotherapy is briefly recalled, and she emphasizes the ethical laws of the chartered physiotherapist, which bind her to work only under a registered medical practitioner. She makes a plea for the close co-operation of the doctor and the physiotherapist. In the following chapters she outlines the various forms of treatment which the chartered physiotherapist is trained to give, rightly emphasizing the value of active movement. She advocates massage and various forms of electrotherapy with the keenness of one who is an expert practitioner of these arts, and, while there is a welcome tendency to make it clear that there are things that such forms of treatment cannot be expected to do, their positive effects are naturally advanced with some enthusiasm. The chapter on "Manipulation by the Physiotherapist" will not be accepted with equanimity by all the medical profession.

Finally, we are presented with a list of conditions for which certain forms of physiotherapy are advocated. This covers more than 200 conditions, ranging from purulent keratitis to haemorrhoids. We are told that in mucous colitis galvanism to each iliac fossa and salicylic ionization of the rectum have proved useful. Such statements will undo much of the good impression given by the early chapters, and the addition of the list of conditions containing such extraordinary prescriptions detracts from the value of the book.

WILLIAM TEGNER.

Artrite Reumatóide, by Jacques Houli (Rio de Janeiro: Tese de Concurso de Livre Docência de Clínica Médica; N.P., 1953), is a study of rheumatoid arthritis and is based on 100 patients. In these days of big battalions of cases this may seem a small number, but the work has been done thoroughly and much consideration given to most points: nevertheless, in a disease so variable and so widespread, numbers tell. There is not much information about cardiovascular complications, for instance. The remarks on Still's disease are based on two examples. The syndrome of Felty likewise has been treated very briefly. The author has studied the literature of the subject thoroughly; there are over 500 references; some are just apt quotations, reaching back to Garrod one hundred years ago. Perhaps the quotations from the literature outweigh the personal observations. The photomicrographs are good; the skiagrams less so. Unfortunately there is no index.

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FAT AND THROMBOSIS

The suggestion that there may be some association between lipaemia and thrombosis is not new, and evidence that such an association is at least possible has been accumulating for many years. Most of the evidence has been rather indefinite, and consequently the subject has not received as much attention as it would now appear to deserve. Information about thrombosis in general and about coronary thrombosis in particular is of special interest to all medical men, for the death rate from coronary thrombosis is high among members of the profession. It is little comfort to reflect that the apparently high incidence may be partly due to better diagnosis; the risk is still a grave one.

It has long been known that there are a number of conditions in which both lipaemia and thrombosis are commonly found. These include acute blood loss, pregnancy, diabetes mellitus, leukaemia, and ether anaesthesia.[1-3] In all these conditions, however, other factors might well be responsible for thrombosis, and on evidence of this kind alone it would be unjustifiable to infer that there is any causal connexion with lipaemia. Rather less indirect evidence pointing the same way comes from some studies linking thrombosis with dietary fat intake. Dock[4] maintained that men who are neither diabetic nor hypertensive but who subsequently develop myocardial infarction often consume diets rich in butter, cream, and eggs. Malmros[5] and Closs and Dedichen[6] have both called attention to a striking difference between Norway and Denmark during the war. In Norway there was a great reduction in dietary fat intake and a marked fall in the incidence of myocardial infarction. In Denmark both fat consumption and the prevalence of myocardial infarction continued at their usual high level.

One serious difficulty in studying the pathology of coronary occlusion seems to have been cleared away by the work of Professor Duguid and his colleagues. At necropsy gross coronary atherosclerosis is an invariable finding, whereas evidence of recent thrombosis is sometimes not obvious. Hitherto the orthodox teaching has been that atherosclerosis is a degenerative process arising within the arterial wall. This was Virchow's contention, and it has gone unchallenged for many decades. But in fact Rokitansky had previously taught that an atheromatous plaque developed from something deposited on the inner wall of the vessel, and it now seems that Rokitansky was right. Professor Duguid has shown in a careful series of histological studies that a thrombus adherent to the inner arterial wall becomes organized and covered with a cellular layer morphologically indistinguishable from the normal intimal lining. As the process of organization continues, the deposit becomes flattened and the lumen resumes more or less its circular outline. Thus, if the earlier stages have not been observed, the ultimate appearance suggests the development of something within the wall of the artery rather than the organization of a deposit originally lying wholly within the lumen. Many of these organized mural thrombi undergo fatty change and come to show the characteristic appearance of an atheromatous plaque. Such a process has been reported by Duguid in the coronary arteries[7] and in the aorta,[8] by Harrison in the pulmonary arteries,[9] and by Duguid and Anderson in arterioles in cases of hypertension and diabetes.[10] The observations on aortic atheroma have been confirmed by Crawford and Levene,[11] who carefully followed the changes by histochemical methods. It therefore seems reasonable to look for a common cause or group of causes for both thrombosis and atherosclerosis.

In view of these facts evidence of an association between lipaemia and atherosclerosis is relevant in discussing the relationship between lipaemia and thrombosis. A strong suggestion that such an association exists has been one outcome of work on plasma cholesterol levels in atherosclerosis. Anitschkow[12] showed that rabbits fed with large amounts of cholesterol develop arterial lesions resembling human atheroma. In man there seems to be no connexion between dietary cholesterol intake and atherosclerosis,[13] but on the other hand high plasma cholesterol levels are undoubtedly associated with atherosclerosis.[14-20] Variations in plasma cholesterol levels seem to be closely associated with

[1] Joslin, E. P., *Ann. clin. Med.*, 1927, **5**, 1061.
[2] Boyd, E. M., *J. clin. Invest.*, 1934, **13**, 347.
[3] Pernokis, E. W., and Freeland, M. R., *J. Lab. clin. Med.*, 1941, **26**, 1310.
[4] Dock, W., *J. Amer. med. Ass.*, 1946, **131**, 875.
[5] Malmros, H., *Nord. Med.*, 1949, **42**, 1785.
[6] Closs, K., and Dedichen, J., *Lancet*, 1949, **2**, 1242.
[7] Duguid, J. B., *J. Path. Bact.*, 1946, **58**, 207.
[8] —— Ibid., 1948, **60**, 57.
[9] Harrison, C. V., ibid., 1948, **60**, 289.
[10] Duguid, J. B., and Anderson, G. S., ibid., 1952, **64**, 519.
[11] Crawford, T., and Levene, C. I., ibid., 1952, **64**, 523.
[12] Anitschkow, N., *Arteriosclerosis*, by E. V. Cowdry, 1933, New York, p. 271.
[13] Keys, A., *et al.*, *Lancet*, 1952, **2**, 209.
[14] Boas, E. P., *et al.*, *Amer. Heart J.*, 1948, **35**, 611.
[15] Gubner, R., and Ungerleider, H. E., *Amer. J. Med.*, 1949, **6**, 60.
[16] Duff, G. L., and McMillan, G. C., ibid., 1951, **11**, 92.
[17] Gould, R. G., ibid., 1951, **11**, 209.
[18] Keys, A., *Johns Hopk. Hosp. Bull.*, 1951, **88**, 473.
[19] —— *J. Amer. med. Ass.*, 1951, **147**, 1514.
[20] Katz, L. N., *Circulation*, 1952, **5**, 101.
[21] Macfarlane, R. G., *et al.*, *J. Physiol.*, 1941, **99**, 7P.
[22] Fullerton, H. W., *et al.*, *British Medical Journal*, 1953, **2**, 250.
[23] Duncan, G. G., and Waldron, J. M., *Trans. Ass. Amer. Phys.*, 1949, **62**, 179.
[24] Waldron, J. M., *et al.*, *Gastroenterology*, 1951, **17**, 360.
[25] Tulloch, J. A., *et al.*, *Amer. J. Med.*, 1953, **14**, 674.
[26] Morris, J. N., *Lancet*, 1951, **1**, 69.

alterations in dietary fat intake, and moreover in populations living on a high-fat diet the average plasma cholesterol level increases steadily with age.[13] Thus the most likely explanation of these observations is that a high dietary fat intake is linked with atherosclerosis.

Studies on the part played by fatty substances in blood coagulation provide yet another approach to the same problem. Macfarlane and his colleagues[21] showed that plasma freed from fat by high-speed centrifuging or by carbon tetrachloride extraction lost its power of coagulation in the presence of Russell's viper venom. The defect could be restored by a number of fatty substances, including even cream from the top of a milk bottle. A distinction of importance is that blood coagulation and thrombosis are different processes: the only undoubted similarity between them is the final formation of fibrin. Nevertheless, the efficacy of anticoagulant drugs in thrombotic conditions suggests that at least part of the mechanism is common to both processes. Therefore the paper in this *Journal* last year by Fullerton, Davie, and Anastasopoulos[22] showing that fat ingestion has a direct effect on blood coagulation reported an advance of fundamental importance. They found that a breakfast of bacon and eggs and bread-and-butter was followed by a shortening of the accelerated plasma clotting time with Russell's viper venom, and a shortening of the whole-blood clotting time in siliconed tubes. Similar results had been reported following cream ingestion by Duncan and Waldron[23] and by Waldron *et al.*,[24] but Tulloch *et al.*[25] have shown that part at least of the change reported was due to failure to use clean syringes for successive venepunctures. However, Tulloch and his colleagues seem to have gone too far in concluding that "the blood clotting time is not altered by the oral administration of cream." They decided quite arbitrarily that any shortening of the clotting time by less than 30% would be disregarded. In fact, by the usual criteria of statistical significance they have convincingly demonstrated that a change occurs.

Thus there is a considerable body of evidence which seems to show that lipaemia is a factor in the causation of thrombosis. It is clearly not the only factor of importance. Morris[26] claimed that coronary atherosclerosis was if anything less common than formerly, while deaths from myocardial infarction appear to be on the increase. Some different explanation is required for this observation. Again, the higher incidence of myocardial infarction in bus drivers than in bus conductors is most unlikely to be associated with any difference in fat consumption. But at least it is evident that a number of promising lines of inquiry are opening up in what has appeared until recently to be a depressingly unrewarding field for investigation.

CIVIL SERVICE DOCTORS

The pay increases for three grades of medical officer in the Civil Service which have just been agreed (see *Supplement*, p. 194) are the outcome of over four years' protracted negotiation. It was in August, 1949, that a joint committee of the B.M.A. and the Institution of Professional Civil Servants first lodged a pay claim with the Treasury on behalf of Civil Service M.O.s. This claim was turned down in the following February. In the summer of 1950, however, anxiety over recruitment, already at an increasingly low ebb, and a serious shortage of doctors in the Civil Service, forced the Treasury to take some action, and it moved in the natural way of things towards setting up a committee of inquiry (the Howitt Committee[1]). If the 650-odd doctors in eighteen Government departments expected anything from this committee their expectations were rudely shattered by the trifling increases which it recommended in November, 1951. As we said in a leading article at the time,[2] "It [the Howitt Committee] is content to advocate salaries that are second-best when the Civil Service ought to be attracting men of the highest quality for these important posts." The B.M.A. supported the joint committee in its refusal to advise Government medical officers to accept the Howitt Committee recommendations, and in February, 1952, the Council of the Association decided to refuse to advertise Civil Service medical appointments in the *Journal*. This decision was ratified by the Representative Meeting of that year. Reluctantly the Treasury in due course entered into direct negotiations with the Joint Committee, which, in its turn, has kept the Council of the B.M.A. fully informed at every stage.

The conditions of the agreement are fully set out in this week's *Supplement*. It will be seen that both sides will be free to make representations to the Royal Commission on the Civil Service, which is now sitting, particularly on the rates of pay for senior and principal medical officers, whose increases in the present agreement are regarded by both sides as purely token. Furthermore, the Joint Committee, which will continue to act for the Civil Service M.O.s on behalf of the B.M.A. and the Institution of Professional Civil Servants, is free to ask the Royal Commission to consider its full claim for the medical officer grade or, for that matter, any grade. Whatever recommendations may come from the Royal Commission—and there can be no doubt that the need for attracting recruits of high quality to this small but important branch of our profession will be well in its mind—the B.M.A., working through the Joint Committee, has in its persistence in a right cause achieved a

[1] *Report of the Committee on Pay and Organization of Civil Service Medical Staffs*, 1951, H.M.S.O.

[2] *British Medical Journal*, 1951, 2, 1206.

notable feat in moving an unyielding Treasury on behalf of a minority of its members, even though it did not move it all the way.

STRUCTURE AND LIFE

Scientific knowledge of proteins indirectly influences practical medicine at many points. The preparation of immunizing toxoids from toxins is a manœuvre of protein chemistry; the use of plasma transfusion substitutes rests on appreciation of the nature and role of the natural plasma proteins; and some hormones, such as A.C.T.H. and insulin, are proteins, and their manufacture and the possibility of synthetic substitutes depend on protein chemists. Collagen is a protein fibre, and full knowledge of its structure might shed light on "collagen diseases," on the puckering of scars, and on keloids. Myosin and actin are the "contractile" proteins of muscle, and even if the treatment of myopathies were not helped by such study it would still be interesting to know precisely how a muscle contracts, or what happens when a spermatozoon lashes its tail. The genes on the chromosomes of the cell nucleus are made of nucleic acid; the treatment of many diseases might be changed if it was known how the nucleic acid molecules reproduce themselves at each cell division and how they exert their genetic influence. It is therefore not surprising that the research on the structure of proteins and nucleic acids is a big part of the programme of post-war science.

Chemists are beginning now to be able to say how all the amino-acids are arranged in sequence in the peptide chains which form a protein molecule. Sanger at Cambridge was recently able to do this for insulin. But how the peptide chains are arranged together in the three dimensions of insulin, or any other protein molecule, is altogether a more complex unsolved problem. Physicists, however, are beginning to find an answer with the help of *x* rays. Just before the first world war it was found that a single inorganic crystal, such as that of common salt, reflected and diffracted a beam of *x* rays, so that little beams emerged from the crystal in many directions to give a pattern of spots on a photographic film arranged round it. This was entirely analogous to the way a diamond (a crystal of carbon) or cut glass breaks up a light beam into a number of sparkles. But, whereas the directions and intensities of the light sparkles depend on the cut of the crystal surfaces, the emergent spots of *x* rays depend on the arrangement of atoms inside the crystal. With simple crystals it is fairly easy from measurement of the directions and intensities of the emergent beams to deduce what the atomic structure of the crystal must be to give such a diffraction pattern. With a complex crystal, such as that of insulin or haemoglobin, containing perhaps 10,000 atoms in each molecule (as against the two of common salt), a pattern is certainly obtained, indicating that the crystal has an ordered, repeating, atomic structure, but it is a very complex one, with over 2,500 reflections, which so far defies complete mathematical analysis. There are various ways of tackling this problem. One is purely mathematical, seeking new descriptive analytic methods. Another is theoretical: one formulates a possible structure for the molecule, deduces what kind of pattern such a structure would give, and compares this pattern with the one actually obtained. The structure of penicillin was settled thus by *x*-ray diffraction study, since the pattern obtained agreed with only one of the several possible formulae put forward by organic chemists. A third approach is experimental, studying how the diffraction pattern changes when the crystal is gently dried, or when mercury atoms are combined with the free sulphydryl groups in the protein.[1]

Such methods have been extended to substances not obviously crystalline, such as hair, muscle, and collagen. These do give diffraction patterns of a kind with *x* rays, which means that they must have some degree of order or arrangement within them on an atomic or molecular scale. From the pattern obtained it is possible to say that there are regularities which repeat themselves every 1.5 A, 2.86 A, or 5.1 A (or whatever it may be: 1 A$=10^{-8}$ cm.), and the problem is to decide what it is which repeats with this regularity in the molecular structure. There have been various theories, but Pauling and Corey's proposal that fibrous proteins are peptide chains coiled in a tight spiral known as an α-helix at present holds the field.[2] Thus in collagen the chain would make one complete turn every 3.7 amino-acid lengths along it, and each turn would be 1.5 A from the next. Nucleic acids also appear to be fibrous in the natural state. Members of the Medical Research Council's Biophysics Research Unit at King's College, on the basis of *x*-ray diffraction pictures, have proposed[3] a special ribbon structure, the two edges formed by chains of alternating desoxyribose (sugar) and phosphate radicles held together by cross-links of purine and pyrimidine units. Their theory is not only in accord with *x*-ray and chemical data, but explains how variations in the same general structure could give rise to different nucleic acids, specific genes, and mutants, and how the gene may reproduce itself. It may suggest, too, how a virus reproduces itself, and therefore the kind of chemical to destroy it.

[1] Bragg, W. L., and Perutz, M. F., *Proc. roy. Soc. B.*, 1952, **213**, 452.
[2] Kendrew, J. C., *Nature* (*Lond.*), 1954, **173**, 57.
[3] Watson, J. D., and Crick, F. H. C., ibid., 1953, **171**, 964.

THE TREATMENT OF VOMITING

Even healthy people after mild dietary indiscretion find nausea and vomiting unpleasant. How much more distressing it is when it occurs as part of some general disease, or, as so often, during recovery from the combined effects of an operation and anaesthetic. Efforts to prevent or treat vomiting have not been lacking through the centuries. The literature of the last fifty years in particular reports a large number of remedies, each one, in the opinion of its sponsor, a certain specific. The substances which appear in this list are as diverse as iodine, insulin, glucose, olive oil, chloretone, and dimenhydrinate ("dramamine"). The causes of vomiting are many, and most approaches to its treatment in the past have been along the rational line of diagnosis and treatment of the causal factor. In some papers the blame is laid on the temperament of the patient, and such "vomiting-prone" patients receive little more than a shrug of the shoulders. In others, it is the fault of the disease, of the surgeon, of the anaesthetist, or of something else. There is truth in all these observations, for there is little doubt that some people are nauseated more easily than others. Many operations on the abdominal viscera are more likely to be followed by vomiting than operations on, say, the foot; ether is more apt to cause vomiting than nitrous oxide.

Two recent papers on this vexing problem advocate drugs structurally belonging to the general group of antihistaminics. The first[1] reports diphenhydramine hydrochloride ("benadryl") given intravenously. The authors consider it to be a good prophylactic against post-operative nausea and vomiting when administered intravenously just before the induction of anaesthesia, and also a good method of stopping vomiting when given in the post-operative period. It has also been reported that the vomiting associated with general disorders such as chronic nephritis, chronic pyelonephritis, subarachnoid haemorrhage, pregnancy, and gastro-enteritis is relieved for varying times. The well-known major side-effect of diphenhydramine—namely, drowsiness—occurred in some cases; in others stupor, visual hallucinations, muscular twitchings, dryness of the mouth, and phlebitis were also seen, although they were not considered to be serious disadvantages. This paper confirms the anti-emetic properties of diphenhydramine already demonstrated by many others, notably Glaser and Hervey.[2]

The other recent report[3] concerns the controversial substance chlorpromazine, known commercially as "largactil." It has already been shown that this substance could overcome the emetic effect of apomorphine.[4] Now it is reported as being used successfully in a wide variety of conditions in which vomiting is a prominent feature. These include carcinomatosis, labyrinthitis, lymphomatosis, and uraemia. Chlorpromazine was also apparently effective in preventing or controlling vomiting caused by "antabuse" administration to alcoholics and that associated with therapy by aureomycin, codeine, morphine substitutes, and morphine itself. The only side-effects reported are dryness of the mouth, mild sedation, and occasional faintness, palpitation, and flushing of the face.

There seems, therefore, to have been some change of opinion on the prevention and treatment of nausea and vomiting. The attempt to distinguish specific aetiological factors and to treat them seems to be giving way to the practice of administering drugs believed to have an anti-emetic effect independently of the cause of the vomiting. Another observation on this subject may be timely. The evaluation of an anti-emetic drug is not an easy matter and should not be lightly undertaken without careful preparation. Of the many reports through the years, most are of little value because the design of the experiments has been poor and statistical treatment of the data either suspect or not carried out. Two papers within recent years might be cited as examples of the way anti-emetics should be studied. In both the design and tests of significance were adequate. One paper, by Gordh and Rydin,[5] described an investigation into cerium oxalate, the other, by Mushin and Wood,[6] an investigation into the effect of nicotinic acid on post-operative vomiting. Both showed that the drugs in question had no significant effect on the incidence of vomiting. The latest reports on diphenhydramine and chlorpromazine do not indicate that the experimental observations were planned along these lines.

[1] Warrington, W. R., *et al.*, *Surgery*, 1953, **34**, 837.
[2] Glaser, E. M., and Hervey, G. R., *Lancet*, 1951, **2**, 749.
[3] Friend, D. G., and Cummins, J. F., *J. Amer. med. Ass.*, 1953, **153**, 480.
[4] Laborit, H., *et al.*, *Presse méd.*, 1952 **60**, 206.
[5] Gordh, T., and Rydin, H., *Anesthesiology*, 1946, **7**, 526.
[6] Mushin, W. W., and Wood, H. M., *British Medical Journal*, 1944, **1**, 719.

SYNTHETIC DETERGENTS

Synthetic detergents, though overcoming some of the imperfections of soaps and alkalis used as cleansing agents, especially in hard water, have introduced some new difficulties of their own. Last year the Minister of Housing and Local Government appointed a committee under the chairmanship of Sir Harry Jephcott "to examine and report on the effects of the increasing use of synthetic detergents and to make any recommendations that seem desirable with particular reference to the functioning of the public health services." The committee's full report on the subject will not appear until further extensive investigations have been carried out, but an interim report[1] has now been published which contains some fairly reassuring information. It seems that despite the widespread use of detergents the incidence of dermatitis of the hands has not increased—a finding supported by recent evidence[2] from the U.S.A. But these substances may irritate some skins—for instance, the washing of babies' napkins in strong detergents can cause a contact dermatitis of the napkin area—and the committee advises that, after their use, the hands should be thoroughly rinsed in fresh water and dried. The wearing of household rubber gloves is a sensible precaution which should be taken by housewives whose hands become rough and sore from constant immersion in water—which, as the committee points out, often contains much more detergent than is really necessary. So far there has been no evidence of any

[1] Interim Report of the Committee on Synthetic Detergents, 1954, H.M.S.O.
[2] Sture, A. M. J., *et al.*, *Arch. Derm. Syph. (Chicago)*, 1953, **68**, 643.

ill effects from the possible ingestion of minute traces of synthetic detergents left on crockery, but it is a good hygienic practice to rinse all utensils in hot water before draining.

Housewives as a whole are said to prefer the types of detergents which produce foam, though this quality is unrelated to degreasing and cleaning power. Unfortunately foaming is persistent, and at sewage disposal works, especially where the activated sludge method is used, foam may rise to several feet. This is a serious inconvenience and actual danger to the operators, and the foam may drift and be offensive to the neighbourhood because of contained particles of unpurified sewage matter. Drifting foam can also have a blanketing effect on vegetation. The committee views with concern the possibility that the increasing use of detergents may make it more difficult for sewage works to produce effluents up to the required standard of purification. Since some of the constituents of detergent preparations are only partially removed or destroyed during sewage treatment, further investigation is being carried out to assess how far the presence of these materials is likely to harm river life or river-drawn water supplies. However, the committee thinks that the problem of foaming at sewage works, though calling for speedy solution, is not sufficiently serious to warrant alarm.

FAITHFUL SERVICE

It is a happy characteristic of medicine that its tradition of service readily infects all who come in intimate contact with its work. This is particularly noticeable in that devoted band of lay helpers—yearly increasing—who without regard for the clock, day in day out, smooth the doctor's burden for him and ease his lot. It is true to say that these people, secretaries, receptionists, and surgery assistants, can make or mar a practice, and it is very seldom that they do the latter. It is good news in this week's *Supplement* (p. 194) that the B.M.A., through the Medical Insurance Agency, has sponsored a pension and sickness scheme for doctors' employees. It will satisfy a long-felt need and will enable medical men and women to fulfil in a business-like way obligations which they have always sincerely felt but have been at a loss to know how to carry out.

BIRDS AND VIRAL ENCEPHALITIS

Birds have long been recognized as the source from which man is occasionally infected with psittacosis, or with other viruses of the ornithosis group, usually by the inhalation of infective material. Recent reports from Japan,[1] Australia,[2 3] and Malaya suggest that birds may also be the carriers of certain viruses which cause encephalitis in man. West Nile viruses and those causing St. Louis encephalitis, Japanese B encephalitis, and Murray Valley encephalitis (M.V.E.) are serologically related: no information is available on the epidemiology of West Nile virus infections, but the other three viruses have several features in common in addition to their similar size and shared antigens. For example, the proportion of subclinical to clinical infections in man is high; they are transmitted by culicine mosquitoes; and birds are highly susceptible to infection with the viruses, and usually show a transient high-titre viraemia, but no clinical symptoms.

The most obscure feature of the epidemiology of all these diseases is the reservoir of the virus during the winter, or, in the case of M.V.E. virus and Japanese B encephalitis virus in Japan, the reservoir from which the virus periodically invades areas in the temperate zones. Investigation of this problem demands what Dr. J. R. Audy, in a paper appearing elsewhere in this issue, describes as a biological approach to medical geography. Two hypotheses have been suggested, both of which bring birds into the foreground of the picture. Australian workers have suggested that persistence of M.V.E. virus is confined to areas near the Tropics where vector mosquitoes are present throughout the year. The appearance of the disease in temperate regions during the summer is thought, on this hypothesis, to be due to bird movement through a region in which vector mosquitoes were present. A migratory bird might well be infected in one place and develop viraemia a week later in another place hundreds of miles away, and thus infect local mosquitoes with the virus. These mosquitoes could then infect local birds and establish a new focus of infection. The appearance of M.V.E. in southern Australia at long intervals of time might then be due to exceptional meteorological conditions which may cause exceptional bird movements.

The other view derives from the isolation[4] of St. Louis encephalitis virus from chicken mites (*Dermanyssus gallinae*) collected in St. Louis County during a non-epidemic period. In contrast to the negative results obtained with mosquitoes, the transmission of infection through the eggs of ticks and mites (and hence the possibility of indefinite survival apart from vertebrate hosts) has been reported with several viruses, and Smith and his colleagues[5] have shown that the eggs of *Dermanyssus gallinae* can harbour the virus of St. Louis encephalitis and that larvae hatched from the eggs can transmit the infection. Thus St. Louis encephalitis virus may survive the winter in the mites of domestic fowls and other birds. In view of the close similarities in the biological behaviour of the other three related viruses, it is possible that a similar cycle may occur with them also.

Both hypotheses may ultimately prove correct. A mite–bird cycle may provide the reservoir of some of these infections in tropical regions: bird migration, annual or exceptional, could then result in the infection of birds in more temperate areas, with a consequent overflow of infection into the susceptible local human populations. The ultimate reservoir of Japanese B encephalitis and Murray Valley encephalitis may be best sought in tropical regions such as Malaya rather than in Japan and Australia, where the clinical diseases were first recognized.

[1] Hammon, W. McD., Reeves, W. C., and Sather, G. E., *Amer. J. Hyg.*, 1951, **53**, 249.
[2] Miles, J. A. R., and Howes, D. W., *Med. J. Aust.*, 1953, **1**, 7.
[3] Anderson, S. G., and Eagle, M., ibid., 1953, **1**, 478.
[4] Smith, M. G., Blattner, R. J., and Heys, F. M., *Science*, 1944, **100**, 362.
[5] —— —— —— and Miller, A., *J. exp. Med.*, 1948, **87**, 119.

Sir Russell Brain was re-elected President of the Royal College of Physicians of London on April 12. He was first elected President of the College in 1950.

CLINICAL PATHOLOGY IN GENERAL PRACTICE

LABORATORY INVESTIGATIONS IN SUSPECTED INDUSTRIAL POISONING

BY

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There are two situations in which a general practitioner may need the help of the laboratory in dealing with patients he suspects to be suffering from industrial poisoning : (1) When the history and clinical picture point to industrial poisoning but he has no direct evidence of such exposure, nor of its magnitude ; here both doctor and patient may be unaware of any danger in the patient's work, and a laboratory investigation may be the only way of establishing that exposure has occurred. (2) When the doctor is supervising (as an industrial medical officer) the health of a group of workpeople ; here the fact of their exposure is known to him, but laboratory tests are required to estimate its degree and identify individuals who are running into danger.

Only a few industrial poisons give rise to specific laboratory findings. The toxic metals can be detected in the body fluids, and carbon monoxide gives rise to a characteristic change in the haemoglobin. Investigations of this nature require not so much an experienced biochemist as a biochemist experienced in the particular technique, as well as a laboratory set aside for the work (the determination of lead in biological fluids provides a good example). These conditions can rarely be fulfilled in general hospital laboratories. In consequence it has been the practice in some regions to attempt to concentrate work of this nature in one or two special laboratories. Unless special facilities of this type are available results may be inaccurate, and it cannot be too strongly emphasized that incorrect results are worse than no results at all. The clinician, therefore, should explore the facilities available to him before requesting unusual investigations to assist him in diagnosis.

The more important use of laboratory investigations in those exposed to industrial poisons lies in prevention. Unfortunately, this work does not fall within the ambit of laboratories associated with the National Health Service, and the practitioner requiring these examinations will have to make special arrangements. Large firms usually establish a laboratory to deal with their own particular health problems, but difficulty arises where the numbers of workmen involved make such provision uneconomical.

It is often possible for the research biochemist to devise tests which will enable a check to be kept on workers exposed to particular poisons. But the methods to be used and the interpretation of results in the prophylactic field raise special problems, and general practitioners wishing to institute this type of routine supervision would be well advised to seek the advice of an expert in industrial medicine.

Whether the laboratory test is to be used for diagnostic or prophylactic purposes it must be carried out with due care, and this may involve much labour in the laboratory. Equal care is necessary, however, in the collection of specimens, and the practitioner would be wise to consult the laboratory about their tests and the times at which unusual specimens should be submitted.

Details of some of the industrial poisons giving rise to specific changes are briefly discussed below.

Lead-Poisoning

Lead-poisoning still continues to occur and the diagnosis is often missed. Help can be obtained from laboratory investigations provided these have been carried out in a suitable laboratory. In detecting minute quantities of lead in body fluids the biochemist has to take the greatest care ; reagents must be "deleaded" and special glassware used. The latter is prepared by washing with pure hydrochloric acid and rinsing with water twice distilled from all-"pyrex" apparatus. All these time-consuming precautions in the laboratory, however, are of no avail if proper care has not been observed in the collection of samples by the practitioner.

Lead in Urine.—A true and uncontaminated 24-hour sample would theoretically be most suitable, but in practice the collection of spot samples of at least 200 ml. is to be preferred. The urine should be passed direct into all-glass stoppered pyrex flasks (with or without the use of a pyrex funnel). Great care must be taken to avoid contamination of the specimen from lead on the clothing. To avoid the addition of trace metals *no* preservatives must be added. The normal lead content of urine ranges up to 100 μg. per litre. Values in excess of this are found in nearly all lead-workers and no particular level can be taken as indicating poisoning. Raised urinary excretion of lead merely indicates raised absorption and confirms what may be already known, that the patient is a lead-worker. Low-grade absorption will give a urinary figure of up to 150 μg. per litre and suggests good working conditions. Repeated values of 200 μg. indicate substantial absorption. If values are frequently found above 300 μg. absorption is excessive and poisoning may occur at any time. There is considerable daily variation in urinary lead output and reliance should not be placed on single observations. In the supervision of lead-workers the importance of group trends cannot be overemphasized. A high lead level in urine in an individual does not indicate poisoning, nor does a low one completely rule it out. Diagnosis must rest upon the clinical picture taken in conjunction with all laboratory findings.

Lead in Faeces.—This investigation has no place in the detection of individual cases of industrial lead-poisoning and is of little value in assessing an industrial hazard.

Lead in Blood.—This determination has been widely used in the United States. Ten millilitres of blood should be collected in a dry all-glass syringe, cleaned as described above, with a stainless steel needle. The blood should be transferred to a similarly cleaned test-tube and allowed to clot. The normal range of values is 0–80 μg. per 100 ml. of blood.

Coproporphyrin in Urine.—While urinary coproporphyrin concentration is a useful index of the lead hazard in groups of lead-workers in industry, the excretion of this substance is also raised in a number of other diseases and the test has little diagnostic importance.

Blood Examination

While by no means entirely specific, blood examination for punctate basophilia offers a useful test for certain types of lead absorption (not lead tetraethyl). Blood for this purpose is most easily obtained from the lobe of the ear. Films should be spread on thin glass slides (to facilitate the use of dark-ground technique in the laboratory). The film should be thin—in a person not markedly anaemic the spreading slide should be at an angle not greater than 20 degrees. It is easier to judge the quality of the film if the slide lies on a white background—a piece of white blotting-paper is very suitable. Several films should be prepared and these should be allowed to dry in air.

Results must be interpreted with care. Actual counts will depend on factors such as the stain used and the experience of the technician. Many laboratory workers content themselves with reporting "punctates per field"; others use even more cryptic remarks such as "numerous." In the absence of other disease likely to produce this condition (pernicious anaemia, malignant disease) punctate basophilia suggests lead absorption. It is observed in minor degrees in most lead-workers, but large numbers of stippled cells—three or four per field, especially if the granules are large—suggest excessive absorption and the possibility of poisoning. Associated with a haemoglobin estimation, and a limited number of lead-in-urine determinations, this method provides a cheap and objective method of supervising lead-workers.

Mercury

The level of mercury in the urine gives a useful indication of the quantity being absorbed. The collection of the specimen is carried out with the same precautions as for lead.

The normal range of urinary mercury is up to 80 μg. per litre and values in excess of 100 μg. are abnormal. Very high values are often found in those exposed to metallic mercury; for instance, values exceeding 1,000 μg. have been found in such a group of workers, and in isolated cases values exceeded 2,000 μg. These men were all at work, but many showed the rather indefinite clinical picture associated with chronic mercury poisoning. Symptoms should be looked for when the value persistently exceeds 300 μg. per litre.

Arsenic

The patient should be sent to the laboratory so that a fresh specimen of urine can be obtained for examination by the molybdenum-blue colour method. Normal urinary arsenic has been given as 170 μg. of arsenious anhydride per litre.

Carbon Monoxide

Carbon monoxide is one of the commoner poisons, both in industry and in the home, and its detection in the blood is often important for medico-legal purposes. The percentage of carboxyhaemoglobin can readily be measured in the laboratory either by the use of reversion spectroscope or by the sensitive palladium-ammonium molybdate method.

Ten millilitres of blood should be collected with a sterile dry syringe and oxalated.* The blood should be transferred under paraffin to a test-tube and more paraffin should be added to fill the tube, which should be securely corked. Shaking should be avoided, the tube wrapped to exclude light, and the specimen taken to the laboratory without delay so that the analysis can be carried out as soon as possible.

The blood takes up carbon monoxide very readily and minor quantities are not noticed. For instance, the blood may contain as much as 5% carboxyhaemoglobin after smoking cigarettes. In a healthy person *at rest* concentrations up to 15–20% may remain undetected. When the carboxyhaemoglobin reaches 30% a throbbing headache and dizziness are likely to appear, at 50–60% the patient becomes unconscious. If 80% of the haemoglobin is combined with carbon monoxide death occurs rapidly.

*The oxalate anticoagulant should preferably be Heller and Paul's solution, which is prepared from 1.2 g. of ammonium oxalate, 0.8 g. of potassium oxalate, and 1 ml. of 40% formaldehyde, the solution being made up to 100 ml. with water: 1 ml. of this solution is suitable for 10 ml. of blood.

Aromatic Amino- and Nitro-Compounds

Aniline, nitrobenzene, and related aromatic compounds give rise to the formation of abnormal haemoglobin derivatives in blood. The erythrocytes of patients who are cyanosed may contain sulphaemoglobin and methaemoglobin, and methaemalbumin may be present in the plasma.

To examine for these, 10 ml. of blood should be withdrawn by syringe and transferred to a tube, where it must be preserved with a mixture of sodium fluoride and thymol,† which acts as a preservative and anticoagulant. Air should be excluded by filling to the stopper with liquid paraffin and the estimation should be made as soon as possible. Sodium citrate should not be used as an anticoagulant as it interferes with the methaemoglobin determination.

Probably about 1% of the total haemoglobin in the red blood cells is normally present as methaemoglobin. It is only when the methaemoglobin concentration reaches levels of approximately 40% that dyspnoea occurs on exertion, although obvious cyanosis may be present at much lower levels. The cyanosis from methaemoglobin clears in a day or two, but that resulting from sulphaemoglobin may persist for several weeks.

Trinitrotoluene

Workers exposed to trinitrotoluene excrete metabolites in the urine which give a positive Webster test. This consists in adding alcoholic potash to an ethereal extract of the acidified urine, when a violet colour appears. This test is of value only in demonstrating—what is usually well-known—that the patient is working with T.N.T.

Benzene

Blood changes following benzene absorption are important but not specific. Leukopenia, anaemia, or even leukaemia may be observed.

New Chemicals

New chemicals are continually being developed for use in industry. When there is any suspicion of their being poisonous it is one of the duties of the research biochemist to devise methods for their detection and estimation in body fluids. If this is impossible he should attempt to devise an indirect method for assessing the degree of intoxication. Some of the newer chemicals used in agriculture illustrate this.

Selective Weedkillers

Dinitro-*ortho*-cresol (D.N.O.C.), which is used as a selective weedkiller, gives rise to poisoning in man. The clinical picture in mild cases is not clear cut, though help in diagnosis can be obtained from the estimation of this substance in the blood. This is a comparatively simple procedure and can be carried out on small samples of blood. It is particularly useful in supervising the health of those whose work involves exposure to the poison.

The practitioner should submit a sample of 2 ml. of blood to the laboratory. This allows of duplicate tests. The sample is best withdrawn from a vein and must *not* be allowed to clot. A 2-ml. syringe with a fine hypodermic needle serves well. The best anticoagulant is heparin, and suitably prepared tubes can usually be obtained from the laboratory. If such a prepared tube is not available, any clean dry tube may be used; clotting should then be prevented by the previous addition of a few crystals of sodium

†One gramme of sodium fluoride mixed with 0.1 g. of thymol crystals: 0.1 g. of this mixture is taken for 10 ml. of blood.

citrate. Accidental contamination of the sample by chemicals on the skin must be carefully avoided by thorough cleansing of the site of venepuncture with spirit. In order to avoid false peak values, samples should *not* be taken within eight hours of the patient's last exposure. It is not necessary to add any preservative, as D.N.O.C. determinations can readily be carried out on whole blood which is over a week old.

Normal values are usually supplied by the laboratory doing the test. Since D.N.O.C. is a cumulative poison and is only slowly excreted, Bidstrup and her colleagues* recommended that a man should be removed from further contact for at least six weeks, if the blood level, eight hours after his last exposure, is 20 μg. per g. or higher.

Organic Phosphorus Insecticides

The organic phosphorus insecticides are now being widely used all over the world. These substances are toxic to man and produce their effects by inhibiting cholinesterase. In order to detect excessive absorption in workmen using these insecticides, it is necessary to estimate the quantity of this enzyme in the blood. This is not a simple procedure but arrangements have been made for it to be carried out in certain National Health Service Laboratories in *suspected cases of poisoning*.†

There are micro-methods for this determination, but the practitioner would be wise (unless advised to the contrary by his laboratory) to submit a blood sample of at least 2 ml. and preferably 5 ml. Should a micro-method be in use and the practitioner be advised to submit small samples such as can be obtained from a finger prick, it is most important to see that the site is adequately cleaned before pricking, since traces of the insecticide in the sample lead to false low cholinesterase readings. Clotting should be prevented by the use of a heparinized tube or sodium citrate (as for D.N.O.C.); oxalate should not be used. No preservative is required, as enzyme activity of the blood is unimpaired even after a few weeks.

In the absence of an agreed international unit of cholinesterase activity, the amount of enzyme is expressed as a "number."‡ The normal range in healthy adults for whole blood is 80–130 units. Signs of systemic poisoning occur when this figure drops to 20–30 units, though a few patients have shown symptoms when the "number" was in the normal range. The results will almost certainly be interpreted for the practitioner by the laboratory according to the scale in use locally.

The greatest value of this test lies in prevention. In this work the wide range in the normal makes it advisable to have pre-employment determinations carried out on men who are about to be exposed to this poison, and they should subsequently be tested at weekly intervals. A marked fall in a man's cholinesterase number should be regarded as a danger sign and he should be removed from further exposure until his enzyme activity has returned to normal. This recovery is not rapid and may well take six to eight weeks.

Next article on Clinical Pathology.—"Tropical Diseases in Britain," by Professor A. W. Woodruff.

Refresher Course Book.—The first collection of articles in the Refresher Course for General Practitioners (fully revised) are available as a book containing 55 chapters, price 25s. Copies can be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

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*Bidstrup, P. L., Bonnell, J. A. L., and Harvey, D. G. (1952). *Lancet*, 1, 794.

†Dr. E. N. Allott, Group Laboratory, Lewisham Hospital, London, S.E.13; Dr. D. H. Fulton, Department of Pathology, Memorial Hospital, Peterborough; Dr. E. M. Darmady, Central Laboratory, Milton Road, Portsmouth; Dr. P. Kidd, Department of Pathology, Royal Infirmary, Worcester.

‡Aldridge, W. N., and Davies, D. R. (1952). *British Medical Journal*, 1, 945.

Reports of Societies

THE CRIMINAL AND THE DOCTOR

The contemporary crowding of our prisons and the frequency with which young men and women are turning to crime for a living have shocked modern society. Lately, also, the publicity accorded to cases of homosexuality and other sexual offences has heightened the demand that vigorous steps should be taken to mend matters. Unfortunately, no two people agree about what should be done. The psychiatrist has one remedy, the police another, and utterances on the subject from the Bench are conflicting. All are agreed, however, on two things: the urgency of reclaiming all those who can be saved from a life of crime, and the need to protect society from those who cannot.

It is against this background that the International Society of Criminology, with the help of Unesco and the British Council, arranged a two-weeks course in London on "Recent Advances in the Study and Treatment of Offenders." The course ran from March 24 to April 13, and brought together lawyers, magistrates, doctors, psychiatrists, police, prison administrators, sociologists, and other interested people. It consisted of lectures and discussions, and visits to prisons, Borstals, approved schools, and other institutions. The course was directed by Dr. DENIS CARROLL, president of the International Society of Criminology, and Dr. HERMANN MANNHEIM, reader in criminology at London University. Below are reported four of the medical contributions. They deal with electroencephalographic studies, hormone treatment of sex offenders, psychotherapy in prison, and "typological" research on adolescents sent to Borstal institutions.

Electroencephalographic Studies

Speaking on "Electroencephalographic Studies of Offenders," Dr. DENIS HILL (senior lecturer in clinical neurophysiology, Institute of Psychiatry, London University) gave a general survey of work in this field. While the electrical patterns found in epilepsy, brain tumour, and other structural brain disorders were different in kind from the normal record, 10% of the general population showed minor differences in degree, and the study of these was only just beginning. These "variant" records did not indicate any gross structural abnormality, and would be considered normal for children or adolescents in whom, under experimental conditions, they could be produced occasionally by emotional frustration. As the personality trait most often accompanying these aberrant records was undue aggressiveness, it was reasonable to suppose they indicated some failure of the brain to mature and reach integrated functioning, with a resulting imbalance and lack of emotional control. Individuals showing such patterns were more susceptible to physiological stresses, such as a low blood sugar, oxygen lack, and alcohol, and they were also less able to tolerate emotional frustration.

Turning to studies of offenders, Dr. Hill emphasized that no connexion could be found between the E.E.G. tracing and antisocial behaviour as such. Nevertheless, in a recent study of young delinquents, only 16% showed normal recordings. In the prison population, 80% of psychopathic personalities showed variant recordings, a similar proportion to psychopaths in mental hospitals, but among the remainder of the prisoners variant recordings were also abnormally frequent, and these variant patterns were related to aggressiveness. Studies of murderers had been negative in those cases where killing was incidental to another offence, but in those cases where there appeared to be no motive, or where the motive was trivial, three-quarters showed variant records, a fact which indicated the need for close investigation in such cases. There was also a surprisingly high incidence of epilepsy among the

murderers studied, though no case had been found in which the crime was related to a seizure. No explanation for this could be given, but there was evidence suggesting that both epilepsy and an abnormal personality could result from brain damage from anoxia or trauma at birth, probably to the temporal lobes, the last part of the brain to mature. Recent studies showed that where slow waves were obtained from this region there was a 50% chance of a general personality disorder, chiefly shown by irritability, aggressiveness, and antisocial behaviour. Apart from such possible birth trauma and other forms of brain disease, all evidence at present indicated that E.E.G. patterns were primarily determined by heredity.

Treatment of Sex Offenders

Discussing the hormone treatment of sex offenders, Dr. R. SESSIONS HODGE (consultant psychiatrist to the South-western Regional Hospital Board) said that sexual offences could be regarded as due to a lack of balance between primitive drives, probably originating in the hypothalamus and other lower brain centres, and the inhibitory effect of the cerebral cortex which normally regulated them and ensured that they received only socially and ethically acceptable outlets. Drugs could be used either to diminish the drives or to increase the cortical control. Amphetamine "alerted" cortical function via the thalamo-reticular diffusion system and probably diminished enuresis or aggressiveness for this reason. Alternatively, one could depress the drives. In cases of aberrant sexual activity, oestrogens could reduce the sexual impulse to a point where the cortex could control it. Progesterone had a similar effect on women, and could also abolish the outbursts of aggressive behaviour that sometimes occurred premenstrually. In treating the homosexual, Dr. Sessions Hodge felt that the best results occurred when the effects of the drug were frankly discussed with the patient, it being made clear that the responsibility for taking the drug, and so for controlling aberrant behaviour, rested with him.

Though hormones could diminish the drive, they could not alter its direction, and the homosexual remained homosexual when the drug was stopped. Psychotherapy therefore remained the most important form of treatment, though if it was to be effective it would need to be given much earlier in life than was the rule at present.

Psychotherapy in Prison

Dr. H. K. SNELL (director of the Prison Medical Service), dealing with administrative aspects of the psychiatric treatment of prisoners, said that where such treatment was recommended by the courts, or later by medical officers of prisons, prisoners were sent to selected establishments such as Wormwood Scrubs, Wakefield, or Holloway. At Wormwood Scrubs most forms of psychiatric treatment were available, and analytic treatment was given by two visiting psychotherapists. This method was time-consuming, and therefore allowed few to benefit. Group therapy was more promising, and perhaps more suited to the type of case met with. At Wormwood Scrubs the 10 men forming the nucleus of those receiving this treatment lived together in a special ward between group sessions, and there was a full programme of activity, including painting and psychodrama, supplementing the prison routine. Though prison discipline was always in the background, the group was encouraged to develop responsibility for disciplining itself, and the standard was high.

Dr. Snell pointed out that only a small proportion of offenders were suitable for psychotherapy, for reasonable intelligence was needed, and there must be a strong and genuine desire for change; this was often not sufficiently recognized by the courts recommending treatment. It was unfortunate that, because of the time involved, little could be done where the sentence was less than six months, for this group might be expected to include men who would benefit most from psychotherapy. But, as in many cases much could be achieved in only a few interviews by a doctor with psychological insight, prison medical officers should be able to give simple psychotherapy. The practice of N.H.S. psychiatrists visiting short-term offenders in prison, who could then continue to attend as out-patients on release, was another way of overcoming this difficulty.

Prognosis after Borstal

Speaking on "Typological Research on Adolescent Offenders," Dr. D. A. OGDEN (medical officer, H.M. Borstal Institution, Portland) said that he had been struck by the errors that were often made in predicting how lads would turn out when they left Borstal institutions. He had therefore taken a sample of 250 lads and divided them into 10 groups according to the predominant reaction to Borstal training they showed. The grouping of the cases was performed by several officials at the institution after a discussion. Medical opinion counted as one vote equal with the others except in one category which included all cases showing mental abnormality high enough to affect normal reaction to training. The lads had been followed up for four years after their discharge, and analysis of the number of reconvictions in each group had shown significant differences. The "adolescent" and "emotionally unstable" types, which gave so much trouble during training, did well in the long run, though the reconviction rate was high during the first year. By contrast the "submissive," who gave little trouble, had a bad prognosis, as did the "egocentric," "the hysterical swindler," and "unethical" types. However, the "shiftless" type, which had done very badly soon after release, had recovered very well over the longer period. Although there was a marked connexion between broken homes and chronic delinquency, it was interesting that the "unethical" type lads who took to crime deliberately, regarding it as a gamble worth the risk, showed good home backgrounds and high mental stability and ability, perhaps indicating a criminal type. Possibly the most striking performance by any of the types was by the one containing the "abnormals," showing only a 30% rate for more than one reconviction. This was markedly better than many other types and strongly encouraged the view that such "abnormal" adolescents could be trained under close medical and administrative co-operation.

Nova et Vetera

THE BIBLE AND MEDICINE

The Bible and Modern Medicine: A Survey of Health and Healing in the Old and New Testaments. By A. Rendle Short, M.D., F.R.C.S. The Second Thoughts Library, No. 9. (Pp. 142. 6s.) London: The Paternoster Press. 1953.

Mr. Rendle Short is widely known as a teacher and writer on surgery and as one of the editors of the *Medical Annual*. His devout little book discusses the differences between the medicine of the Old and the New Testament—which can be summarized by saying that "possession" is very rare in the former and very common in the latter. He considers also the linguistic evidence on whether St. Luke was a trained physician, the nature of possession and of the miracles of healing, the sanitary code of the Old Testament, the interpretation of the word translated as "leprosy," the physical cause of the death of Christ, and the Biblical conception of disease. His treatment throughout is along lines that may reasonably be described as moderately though definitely conservative. His readable and tolerant pages will be of use to the many, like-minded to him, who must often be seeking such a summary.

CHARLES SINGER.

Correspondence

Perforation of the Colon

SIR,—I was very interested to read Mr. Roger Brearley's medical memorandum (*Journal*, March 27, p. 743) on "Spontaneous Perforation of the Colon due to Alkaline Medication" and his ingenious explanation of the perforation. A paper on unusual perforations of the large bowel is in preparation, but it may be of interest to record here a personal case, rather similar to Mr. Brearley's in that perforation of an otherwise normal colon occurred in a patient who had recently developed constipation and who was receiving alkaline treatment for a suspected duodenal ulcer.

A 41-year-old labourer was admitted to hospital in November, 1953, with a six-hour history of very severe pain, sudden in onset, in the lower abdomen. This was preceded for 24 hours by lower abdominal colic and tenesmus. Five weeks prior to this emergency he had had diarrhoea lasting three days. For several years he had had symptoms very suggestive of duodenal ulceration, for which he had been in the habit of taking a self-prescribed bismuth preparation, and during the few months previous to this hospital admission he had developed increasing constipation. General examination showed a very ill man; his abdomen was silent and rigid throughout with diffuse tenderness and release tenderness, both of the latter being most marked just below the umbilicus and in the suprapubic region. No confident diagnosis could be made other than generalized peritonitis, but in view of the maximum median tenderness the possibility of a perforated Meckel's diverticulum was entertained.

At laparotomy purulent free fluid and liquid faeces were found in the peritoneal cavity and a perforation 3.5 cm. by 1.75 cm. was found on the anti-mesenteric border of the apex of the sigmoid colon loop; protruding through the perforation was a hard faecal mass. Many similar faecal masses were present in the rest of the pelvic colon and rectum, but in no sense could the term faecal impaction be applied. The bowel wall adjacent to the perforation was involved in the generalized inflammation but appeared otherwise normal, as did the remainder of the colon and rectum. Treatment, as in Mr. Brearley's case, was by exteriorization of the affected loop through a muscle-split incision in the left iliac fossa using the perforation as a colostomy and drainage of the pelvis. He received aureomycin during his post-operative course, which was satisfactory, and subsequent sigmoidoscopic and radiological examinations of the colon and rectum failed to demonstrate any abnormality. Two months later his colostomy was closed intraperitoneally and to date he has had no further symptoms; barium enema examination has been repeated and shows no lesion in the large bowel. A biopsy specimen from the edge of the perforated ulcer suggested that the ulcer was a chronic one with continued activity rather than acute, and in view of this histology and the operative findings the ulcer was cast on to the scrap-heap of chronic ulcer pathology—the simple solitary ulcer—although perhaps wrongly.

There is little doubt that diarrhoea due to faecal impaction is a not infrequent occurrence after any operation for peptic ulcer, including simple closure of a peptic perforation, and in my experience, limited to acute surgical practice, faecal impaction occurs by far most commonly under those circumstances. As certain alkalis tend to produce dry hard stools, their use may well lead to faecal impaction, as Mr. Brearley has pointed out. Yet, with constipation very common, faecal impaction relatively so, and a large proportion of the population, constipated and otherwise, taking alkaline medicaments over long periods, it is a little surprising that the complication of perforation of the bowel, if due to faecal impaction, does not in fact occur more often. The complication is an exceptional rarity, and Mr. Brearley reports his case as "almost unique." It would have been interesting to know the histology of the edge of the perforation in Mr. Brearley's case.—I am, etc.,

London, W.3. A. J. M. MATHIESON.

SIR,—An interesting account has recently been published by Mr. R. Brearley of large bowel perforation associated with alkaline medication (*Journal*, March 27, p. 743); we wonder if this is as rare as the author claims. A similar case occurred at this hospital in 1951.

A man aged 55, known to have a chronic duodenal ulcer for which he consumed large amounts of bismuth, was admitted because of recent onset of constipation and colicky abdominal pain, superimposed on his ulcer symptoms. While in hospital, on the day of admission, he suddenly developed agonizing pain in the left iliac fossa, with shock and abdominal rigidity. At laparotomy, the stomach and duodenum were intact, but free in the abdominal cavity were large, odourless concretions and free fluid. No site of intestinal perforation was found, but the patient's general condition was too poor to allow an extensive search, and in fact the patient only survived the operation for a short period. At necropsy a small perforation of the sigmoid colon was found, the wall of the intestine being intact throughout.

Perhaps the most striking features of this case were the rapidly developing severe shock, and the failure of treatment, despite early operation.—We are, etc.,

Manchester, 20. M. PEMBERTON. N. F. KIRKMAN.

Whither Neurophysiology?

SIR,—The study of neurophysiology is now recognized as a basic subject in the training of psychiatrists. It might appear logical that those concerned in the treatment of mental illnesses should have a fair knowledge of the normal functions of the nervous system, and perhaps be confident to diagnose neurological disorders on clinical examination. Yet too many psychiatrists are content to leave the organic field to their colleagues, and have little time for the academic approach to nervous function.

Modern ideas on the brain that have resulted from scientific experiment, including the application of electronic techniques, indicate quite clearly that the existence of a "functional" field must be seriously challenged. It is only one step from the activity of the sense organs to the mental experiences of perception, and the neurophysiologist is finding himself in a sphere that was formerly the undisputed territory of philosophers, psychologists, and psychiatrists. A physical basis has now been established for many aspects of emotional behaviour, and in selected lesions of the brain the type of behavioural disturbance can actually be predicted. Psycho-surgery has been accepted as a useful therapeutic tool without any real understanding of its physiological effect; but its acceptance must be regarded as an admission of a mind–body relationship that is only too plainly material. It might be argued that the brain is merely a medium for the expression of mental activity, which itself belongs to some non-material dimension and cannot be dissected by instruments of science. If this view is correct, it is surely an invitation to psychologists and others to join in this problem of the borderline, discard unwanted theories and speculation, and contribute in some practical way by the use of a common terminology.—I am, etc.,

Leeds. P. P. NEWMAN.

Short-term Use of A.C.T.H. in Rheumatoid Arthritis

SIR,—Much has been written about the long-term use of cortisone and A.C.T.H.—some in favour and perhaps more against. Less has appeared in the literature on the value of short courses of these hormones.

There are five main ways in which short courses can perhaps advantageously be applied in this chronic disease: (1) when surgery is necessary during an active phase of the disease; in those cases that flare up after surgery a short course of A.C.T.H. or cortisone may be very helpful; (2) in connexion with the correction of deformity by manipulation, but here intra-articular injection of hydrocortisone is often to be preferred; (3) in tiding over an emergency in a patient with rheumatoid arthritis more or less under control, to cover a period of shock or fatigue, or in convalescence after a severe infection; (4) for the patient that is nearly, but not quite, capable of work, or recently bedridden as the after-effect of an illness, in order to assist rehabilitation to a

slightly higher but vital grade ; and (5) for the patient whose condition in spite of all other treatment, rest, gold, etc., continues to deteriorate.

A questionary has recently been sent to 30 such cases who have received a course of injections of A.C.T.H. gel 20–30 mg. or A.C.T.H. 60 mg. daily for an average period of three weeks, the dose being gradually tailed off. The patients were asked in retrospect their opinions of the effect of their injections on their "rheumatism" and their general health. While realizing that this is an uncontrolled series of cases and only subjective criteria have been used, the results summarized in the table appear of some interest. In assessing these results it must, however, be remembered that all these cases were deteriorating before treatment in spite of several weeks' rest in hospital and having received all other accepted forms of treatment.

	Much Improved	Slightly Improved	Same	Worse	Total
		Joint and Rheumatic Pains			
Directly after treatment	16	9	5	0	30
6 weeks after stopping treatment	8	8	6	8	30
3 months later ..	2	6	6	6	20
6 " " ..	2	3	5	4	14
		General Health			
Directly after treatment	11	12	5	0	28
6 weeks after stopping treatment	11	6	9	2	28
3 months later ..	5	5	8	2	20
6 " " ..	4	2	6	2	14

The results from the questionary, from the point of view of general health and feeling of well-being, on the whole ran in parallel with the answers about rheumatic pain and disability. While feeling that the indiscriminate use of hormonal treatment in rheumatoid arthritis is to be condemned, these figures help to bear out a clinical impression that A.C.T.H. in small dosage for a short time may be of value in some of those cases that are progressively getting worse in spite of, and after utilizing, all other accepted methods of treatment.—I am, etc.,

Bath. G. D. KERSLEY.

Treatment of Pernicious Anaemia

SIR,—A short while ago in this *Journal*,[1 2] and later in the *Practitioner*,[3] I drew attention to a small group of cases resistant to vitamin B_{12} injections and parenteral liver extracts, which can be satisfactorily treated with oral proteolysed liver. Recently I have studied a further similar patient, and, as I think that these cases are important and have a bearing on research into the treatment of pernicious anaemia, I am now reporting the relevant clinical details of this case.

A female aged 41 first reported ill in May, 1953, giving a short history of diarrhoea, vomiting, lower abdominal pain, pallor, weakness, and dyspnoea on exertion. After admission to hospital it was found that there was slight pigmentation of the conjunctivae with pallor of the mucous membranes. No other physical signs were discovered. The following investigations were carried out to establish the diagnosis: red blood cells 1,920,000 per c.mm.; haemoglobin 44%; white blood cells 4,400 per c.mm. The differential white cell count being: polymorphonuclear cells 66%; lymphocytes 23%; monocytes 1%; eosinophils 10%. The marrow was extremely cellular. The red cell precursors consisted almost entirely of megaloblasts, while the myeloid series showed bizarre formation with atypical mitosis and giant metamyelocytes. The megakaryocytes appeared normal. Red cell fragility, within normal limits; direct Coombs test, negative; barium meal, negative; fractional test meal, no acid was found in the stomach, but after an injection of histamine traces of acid appeared; serum bilirubin, 0.5 mg.%; fat balance test, within normal limits.

A diagnosis of pernicious anaemia in relapse was made. Treatment was started with 100 μg. of vitamin B_{12} given by intramuscular injection three times a week, and there was no response after 19 days. The red cell count and haemoglobin concentration continued to fall, so a potent intramuscular liver extract was given in doses of 2 ml. every third day, and within six days a satisfactory reticulocyte peak of 21.4% occurred followed by a steady rise in the red cell count and haemoglobin concentration until the figures reached were 3,500,000 red cells per c.mm. and 60% haemoglobin. She continued to have weekly injections of this preparation and reported at regular intervals to the haematological clinic, where a gradual deterioration in the red cell count and haemoglobin concentration occurred during the next 15 weeks, until the figures reached were 1,540,000 per c.mm. and 38% respectively.

She was readmitted to hospital and fully reinvestigated and similar results were obtained as previously. A diagnosis of megaloblastic anaemia of the Addisonian type refractory to vitamin B_{12} and parenteral liver extracts was made. Shortly after admission to hospital she was saturated with 1 mg. of vitamin B_{12}, followed by 100 μg. three times a week for 14 days, with no haematological response whatever. Proteolysed liver was substituted in doses of $\frac{1}{2}$ oz. four times a day. On the fourth day there was a dramatic reticulocyte response, the figure remaining between 27% and 22% for the next three days. The marrow reverted to a normoblastic state and there was a gradual rise in the red cell count and haemoglobin concentration, and they are now within normal limits.

From a study of these brief clinical details it must be concluded that this is another example of megaloblastic anaemia distinguishable from Addisonian anaemia which is refractory to both vitamin B_{12} and parenteral liver extracts and only responds to proteolysed liver by mouth.—I am, etc.,

Birmingham, 18. R. O. GILLHESPY.

REFERENCES

[1] *British Medical Journal*, 1952, 2, 1204.
[2] Ibid., 1953, 1, 332.
[3] *Practitioner*, 1953, 171, 648.

Clergy and Doctors

SIR,—I wonder if I may, as an ordinary working clergyman of the Church of England, make a humble request for a far greater measure of co-operation betwixt the general practitioner and the parochial clergy. There seems little doubt that of late there has been an increasing awareness of the importance of the spiritual element in the human psyche, and the part it plays in a properly integrated physical and mental life. Yet so often one still encounters those old antagonisms on the part of medical men which are to my mind redolent rather of the 19th than the 20th century. Scathing comments about "the parson" are still made to patients, and letters addressed to them seeking help and co-operation remain unanswered.

If, of course, such conduct is based on a personal knowledge of the inadequacy of the minister and his lack of professional qualifications, much could be forgiven, but too often it is taken for granted that "the parson" is an incompetent without any effort being made to ascertain either who he is or what he is. I respectfully submit that the rift between the Church and the medical profession is one which must be removed if either is to do its appointed work in the healing of "the whole man." As in all "oecumenical movements," however, progress can only be made by a general willingness to take seriously the essential contributions of each to the common task. Similarly it must begin where the bulk of the work is done, in the hurly-burly of parish and practice.—I am, etc.,

Dorset. TONY CLEMENS.

Animal Technicians

SIR,—With regard to your statement in the annotation (*Journal*, April 3, p. 808) that the animal technician should be of equal status with the medical laboratory technologist, while I have great respect for the animal technicians, and much sympathy with their efforts to increase their status, may I point out that they are after all only an offshoot of my profession? You yourself point out that for such workers to have a high standard of education is not important. The medical laboratory technologist must, however, have such an education before being even admitted as a student.

You refer also to the animal technician as "a new type of scientific assistant." The days when the medical laboratory technologist was merely an assistant are long gone—except perhaps in certain university laboratories. The work performed by the technologist nowadays is nearly always done without direction, and the subsequent reports are sent out on his responsibility. In fact he may surely, by now, be regarded as a scientist in his own right—albeit a junior one. A further relevant point is that the care of animals is included as an important part of the syllabus of the intermediate examination of the Institute of Medical Laboratory Technology, and I think it is true to say that the animal technician has only come into being because of the increased status of the medical laboratory technologist. Therefore I think that it must be admitted that, if a careful and unbiased study is made of the work and examinations of the medical laboratory technologist, it will be realized that he is of far higher status than a thwarted "groom or kennel maid."—I am, etc.,

St. Helens, Lancs. A. E. BROWN.

SIR,—With regard to the annotation dealing with "Animal Technicians" (*Journal*, April 3, p. 808), I was staggered by its postulations and inference. To compare the status and training of these no doubt useful people to that of the medical laboratory technologist shows a most ill-informed and, to my mind, ridiculous conception of the work performed in pathological departments.

It must be obvious to all but the most conservative and die-hard of medical men that an extremely large proportion of all laboratory investigations and, in many cases, the interpretation of findings have passed, or are passing, from the domain of the pathologist to that of the technician. It will be found, particularly in the field of blood transfusion serology, that some of the greatest authorities in the country are not medical men but technologists. Doubtless these men would be astounded to learn that the knowledge of a subject which occupies so small a part of their intermediate examination entitles animal technicians to be considered co-equal to themselves. A cursory inspection of the requirements of the Institute of Medical Laboratory Technology would reveal a world of difference to those of the Animal Technicians' Association—a point not overlooked by the Minister of Health in his recent survey of auxiliary services.

Part of the duties of the senior grade technologist is to instruct those duly qualified medical officers who wish to become pathologists. It would seem, therefore, to be more justifiable to state that in many respects the technologist has, or should have, equal status to the pathologist. Since, however, we appear to have taken a retrograde step, after 40 year of progress, it can be taken as an example of the maxim "*Facilis descensus Averno*."—I am, etc.,

Liverpool, 9. F. MATHER.

Intravenous Iron

SIR,—Recent correspondence (*Journal*, March 6, pp. 583–4) suggests that Dr. J. A. Nissim's article (*Journal*, February 13, p. 352) on reactions following intravenous iron therapy was both timely and stimulating. Since 1947, one of us (F. F.) has given approximately 3,000 injections of iron saccharate, mainly in doses of 100 to 200 mg. Fe. The incidence of early, mild reactions was 0.2%, but we endorse Dr. Jeffrey's comments on the importance of an adequate injection technique. The *p*H of iron saccharate solutions is about 9.5 or greater, and they are hypertonic, which explains their thrombogenic and locally irritant properties. Slow administration is desirable, and dilution of the solution in the syringe with blood assists in this respect and reduces the risk of paravenous injection.

Dr. Nissim states that these solutions are stable in blood or plasma *in vitro*, although he has previously observed precipitation on lowering the *p*H of the mixtures.[1,2] We found that rabbits' plasma containing the equivalent of 0.1% Fe as iron saccharate immediately precipitated in the *p*H range of 7.5–7.7, and showed slight turbidity between *p*H 7.8 and 8.2. A plasma iron concentration of 0.005%, similar to that achieved immediately following a single intravenous dose of 200 mg. Fe (as iron saccharate) to an adult, resulted in initial turbidity over the *p*H range 6.5 to 7.0 and marked precipitation between *p*H 6.0 and 6.5. Similar results were obtained at 25° C. and 37° C. These findings might explain the higher incidence of reactions following rapid injection of doses exceeding the recommended maximum of 200 mg. Fe. We suggest that the relative instability of the complex in plasma, as the physiological *p*H is approached, contributes to *in vivo* precipitation in animals and reactions in man.

Nissim refers to Ramsey's[3] suggestion that a sudden increase in reticulo-endothelial activity results in reactions. Although it is true that the administration of certain colloids in large doses to patients is frequently unattended by reactions, we feel that the rate of removal of the colloid, or some fraction of it, by the reticulo-endothelial system might be an important factor. Thus, when an iron complex tends to be unstable in the circulation, its removal is rapid compared with more stable preparations, and the rate of its disappearance is related to toxicity in animals. Since reactions sometimes follow the first administration of saccharated oxide of iron, it is difficult to believe that antigenicity alone is always responsible.

The mean LD_{50} of 313 batches of iron saccharate solution was found to be 238 mg. Fe per kg. of body weight in mice (standard deviation ±72). A standard batch repeatedly tested for five years was found to possess a mean LD_{50} of 231 mg. Fe (standard deviation ±64). It would appear, therefore, that the LD_{50} values of Dr. Nissim's solutions (LD_{50} 180 and 300 mg. Fe/kg. respectively) do not necessarily indicate a significant difference in toxicity and clinical safety. A heated, iron-free, sucrose solution (non-analar) treated as in the preparation of the iron complex, possessed an LD_{50} >17.5 g. sucrose/kg. in mice. It would therefore appear that this component does not contribute significantly to reactions, although acute lethal effects in animals are not always related to factors producing reactions in man.

Finally, we believe that this problem will be overcome by the discovery of more stable iron complexes, and especially solutions suitable for intramuscular administration. Since 1951 we have prepared several new iron complexes, one of which is approximately one-third as toxic in mice as iron saccharate solutions. It also possesses increased *in vivo* and *in vitro* stability and does not precipitate in plasma over a very wide *p*H range. The solution has a *p*H of 6.0 to 7.0 and is isotonic with tissue fluids, whilst containing the equivalent of 5% Fe. It is well tolerated intravenously or intramuscularly and well absorbed by the latter route, producing satisfactory remissions in hypochromic anaemia in animals and man. The detailed results of these investigations will be reported shortly.—We are, etc.,

FRANK FLETCHER.
E. LONDON.
Research Department, Benger's Ltd.

REFERENCES
1 *Lancet*, 1949, 1, 686.
2 *Guy's Hosp. Rep.*, 1953, 102, 164.
3 *British Medical Journal*, 1950, 1, 1109.

Physical Signs of Mesenteric Vascular Occlusion

SIR,—I have recently had under my care two cases of thrombosis of the superior mesenteric artery, which later came to necropsy. In both cases, on examining the abdomen before death, there was a dullness to percussion in the left iliac fossa and resonance in the right iliac fossa and hypochondrium. Although one might expect to find the abdominal wall covering the small bowel dull on percussion due to exudation of fluid into the cavity of the small bowel, it is less easy to explain why the caecum and ascending colon should remain resonant though gangrenous in both these cases. Perhaps it may be merely a question of the greater size and rigidity of the colon.

I should be interested to know whether others have found this a useful physical sign in differentiating the condition from perforated peptic ulcer or general peritonitis.—I am, etc.,

Carshalton, Surrey. J. F. H. BULMAN.

Ferrous Sulphate Poisoning

SIR,—Following the recent cases of pyloric stenosis after ferrous sulphate poisoning, reported in the *Journal* (August 2, 1952, p. 285; November 28, 1953, p. 1200; and January 16, 1954, p. 156), the following case may be of interest.

On December 23, 1946, a boy aged 2½ was admitted to hospital with a history that he had swallowed approximately 25 of his mother's "fersolate" tablets at 12 noon that day. About one hour later he was screaming with severe abdominal pain which doubled him up. Two hours later he became semi-comatose and was brought to hospital. On examination he was very drowsy but could be roused. His stomach was washed out and a brownish fluid obtained. He subsequently had haematemeses at 3 p.m., 4 p.m., and 9 p.m. He then gradually improved, but on January 14, 1947, began to vomit again and peristalsis was observed in the epigastrium. He became dehydrated. He failed to improve on intravenous saline, suction from an indwelling gastric catheter, lavage with sodium bicarbonate, and atropine methonitrate ("eumydrin"). Accordingly, on January 29, 1947, the child was operated on and a posterior gastro-enterostomy performed. The surgeon noticed a dark blue, semi-necrotic mass of mucous membrane occupying only the distal third of the stomach; the upper two-thirds of the gastric mucosa seemed to be fairly normal. He made an uninterrupted recovery. Five years later, March 4, 1952, a barium meal showed that no barium passed the pylorus and that all emptying was taking place by the stoma. I last examined him on January 29, 1953, when he was keeping very well, had no digestive symptoms, and his height and weight were within normal limits. He has also a congenital heart lesion (subaortic stenosis).

This case is similar to those mentioned at the beginning of this letter in that the pyloric end of the stomach was mainly involved, leading to stenosis. I wish to support others who have written to emphasize the need to try and prevent these cases of poisoning with ferrous sulphate. I note that Professor A. G. Watkins and Drs. P. T. Bray and O. P. Gray have seen 15 cases in their department in the past 7 years (*Journal*, February 6, p. 335). It is not sufficient safeguard to state on the label of the bottle that the tablets are dangerous to young children. Dr. I. O. B. Spencer in his excellent article on the subject (*Journal*, November 10, 1951, p. 1112) has suggested wrapping the daily dose separately and securely in small packets, and he mentions that in the German Army Medical Service nearly all tablets were supplied in packets of five. This suggestion seems to have passed unheeded so far by the manufacturers. An alternative suggestion is to make the pills less palatable for children. Some manufacturers now incorporate a bitter substance in the coating of their pills—for example, some of the antihistamine drugs. This practice could be extended to all such pills which have the appearance of children's sweets, and I do not believe this will stop adults swallowing them for therapeutic purposes.

The above case was originally treated by Dr. E. J. Glynn and Mr. N. L. Shepperd. I have only seen the child recently and I thank them for allowing me to publish the details.—I am, etc.,

Bexhill. LESLIE SCOTT.

"What's What's Syndrome"

SIR,—On opening the *Journal* these days we often see case reports of, shall we say, "What's What's" syndrome associated with gout or "Istheresucha's" syndrome with psittacosis, etc. Might I appeal for a definition of the less widely known (e.g., Raynaud's) syndromes by writers referring to them? Too often correspondents either assume that their readers know what they are writing about, or perhaps attempt to impress the less informed. A very recent encyclopaedia is not always at hand to enlighten us, and in one of your recent issues two syndromes were referred to, neither of which is mentioned in a recently published textbook of medicine consisting of over 2,000 pages. Little extra space would be required for a brief statement by your correspondents of what constitutes the syndrome to which they refer. May I enlist their sympathy?—I am, etc.,

Cardiff. LAMBERT ROGERS.

Cancer of Uterus

SIR,—The letter of Dr. Robert P. Towers (*Journal*, March 20, p. 704) and the paper by Dr. J. W. Magner and Professor W. Kearney (*Journal*, February 20, p. 434) on the relative incidence of carcinoma of the uterine body and cervix prompt us to submit the corresponding figures for East Kent, based on material examined histologically during the period January, 1951, to the present day.

One hundred and twenty primary uterine cancers were encountered. Eighty-one were of cervical origin (80 epidermoid carcinomas and 1 adenocarcinoma) and 39 were endometrial adenocarcinomas, 3 showing extensive epidermoid metaplasia. This 2:1 ratio of cervical to corporeal carcinoma occupies an intermediate position between those recorded in most textbooks and those given by your contributors, who found an equal incidence or a preponderance of endometrial tumours. The material was drawn from a mixed urban and rural community which includes the full range of socio-economic groups. Care has been taken to exclude from our totals cases of carcinoma (all cervical) who attended the radiotherapeutic centre from localities outside the specified area.

We feel that our findings are probably representative of the relative frequency of these two types of carcinoma throughout the country, but evidence from other areas is needed before a conclusion on this point can be reached.—We are, etc.,

Canterbury. G. B. FORBES.
Thanet. H. STERNDALE.

Smoking and Mouth Cancer

SIR,—In commenting on my article "Cancer of the Tongue, Mouth, and Pharynx: Sex Differences in Prognosis following Radiotherapy" (*Journal*, February 20, p. 430), Dr. Phyllis Wade, using lung cancer as an analogy, expresses the opinion (*Journal*, March 27, p. 761) that "prognostic differences which appear to be linked with sex or age could be due, wholly or in part, to differences in smoking habit and/or duration of smoking."

Had my observation been limited to this particular study I should have shared Dr. Wade's opinion and added the smoking factor to the other suggestions described as "three obvious lines of inquiry." It seemed to me, however, that, for the situation to be analogous with lung, one would expect to see not only the worse response to treatment already demonstrated in male patients, but also an increased incidence.

It was stated in the article that incidence rates and their changing pattern (based on a population of approximately 4½ million) are the subject of a separate survey in course of preparation. Measured over an interval of a decade by the calculation of a comparative morbidity index to evaluate the effect of changes in the age-constitution of the population, this survey will show a marked decrease in cancer of the tongue and mouth in men, a substantial increase in women (a trend concealed largely in mortality rates because of the better response to treatment), and an appreciable increase in cancer of the pharynx in both sexes.

Faced with these conflicting trends in incidence and behaviour, I felt loath at this stage to put forward smoking habits as a possible explanation of the difference in results between men and women. Nevertheless, although the picture seems rather complex to me at present, this is not to say that Dr. Wade's suggestion may not prove to be a useful line of investigation.—I am, etc.,

Manchester, 20. MARION H. RUSSELL.

Recurrent Intussusception in Children

SIR,—The article by Mr. D. A. Macfarlane and Mr. L. P. Thomas on "Recurrent Intussusception in Children" (*Journal*, March 6, p. 559) prompts me to record the experience with this condition at the Royal Belfast Hospital for Sick Children.

While reviewing the results in 200 consecutive cases of acute intussusception admitted over a ten-year period (1943–52), I found that 12 of these young patients had had recurrences, one little girl having had three separate intussusceptions in as many weeks. In four other cases there were histories very suggestive of a previous attack, but not confirmed by operation. Nine of the 12 proven cases were in boys, and two-thirds of the patients were more than 1 year of age—in the entire series of 200 acute intussusceptions, three-quarters of the patients were aged 1 year or less. The interval between attacks varied from 5 days to 19 months, with an average of 6 months, and in only one case was a possible aetiological agent found at the second operation. Two of the patients had had a brother or sister who also had suffered from intussusception, and in half the cases recurrence took place at a different site. All 12 patients survived, although one boy had a burst abdomen—probably the skin stitches should be left in a little longer than usual to prevent a complete breakdown of the wound. Fraser[1] reported a case (not included here) from this hospital of a girl of 2½ years who had had an intussusception on four separate occasions, and Hipsley (quoted by Clubbe[2]) had a similar case. Wansbrough and Cram[4] have also reported a case which recurred three times, and another which recurred four times, but gave no details apart from stating that the recurrences did not take place in the immediate post-operative period.

Your contributors point out that in most cases the aetiology of intussusception is unknown, and theories blaming weaning, etc., have gained credence more by repetition than by any scientific proof. The enlarged glands so often found in many ways resemble those of non-specific mesenteric adenitis of older children, and if they played any part in the aetiology their continued presence might explain the recurrences. Gross[3] thinks that an enlarged ileo-caecal valve may be responsible and advises the removal of the ileo-caecal part of the bowel if there has been a recurrence, although he is against preventive operations in the treatment of first attacks of intussusception.—I am, etc.,

JAMES KYLE.

Belfast.

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Burns and the Adrenal

SIR,—Dr. H. F. West's criticism (*Journal*, March 27, p. 763) that my paper on "Adrenocortical Function in Burned Patients" (*Journal*, March 6, p. 541) "does little to clarify the indications for cortisone therapy" requires an answer. The uses of cortisone may be divided into two main groups. First, there are uses based on the physiological correction of a known endocrine deficiency, such as in the treatment of Addison's disease, and, secondly, there are uses based on the pharmacological (may I say "non-specific"?) action of the drug in conditions like rheumatoid arthritis, in which there is no evidence of adrenocortical failure.

In the opening sentence of my article I stated: "This paper is concerned with the activity of the adrenal cortex of burned patients, and in particular with a search for evidence of adrenocortical failure arising during the illness"—in other words, with indications for "replacement" therapy. The pharmacological or non-specific use of the drug in burned patients was outside the scope of the paper. In my opinion only a carefully controlled clinical trial, involving many patients, could answer whether cortisone is or is not a life-saving measure in some burned patients. This has not been answered in the enthusiastic reports, mainly from the U.S.A., involving the treatment of a few patients. My information is that the initial enthusiasm has waned as experience has grown. It should not be forgotten that cortisone therapy is not without potential danger. A large burn becomes an extensive open wound infected with various bacteria. The infection is difficult enough to control with modern antibiotics, and cortisone therapy might well increase the number of septicaemic complications and the fatality rate.

Both Dr. West and Dr. J. A. Strong (p. 763) make certain criticisms of the methods I used in determining adrenocortical activity. I agree that any indirect method, including those based on changes in the blood eosinophil count, is open to fallacies. So too are the urinary steroid estimations advocated by Dr. West. While such estimations have their use and place, they are even less reliable than the blood eosinophil count. For example, only a very small (about 1%) and apparently variable fraction of parenterally administered cortisone can be recovered from the urine. Only results based on a satisfactory, *direct* method of determining the changes in the corticoid level of the blood after burning will be free from these criticisms. Such an investigation using polarography is taking place elsewhere in Britain, the results of which will be interesting to compare with my indirect evidence based on the eosinophil count.

Dr. Strong states: "There must be few who regard subcutaneous or intramuscular adrenaline as an adequate adrenocortical stimulus." This is rather surprising, since there is abundant evidence that adrenaline can stimulate the production of A.C.T.H. by the anterior pituitary and thereby induce hyperactivity of the adrenal cortex.[1–5] Indeed, the eosinopenia occurring after subcutaneous adrenaline in some adrenalectomized mice can be correlated with the presence of accessory adrenals or with adrenal remnants[6] and subcutaneous adrenaline is advocated as a test of *completeness* of adrenalectomy.[7] Moreover, adrenaline does not have a direct eosinopenic effect on eosinophil leucocytes, since it fails to reduce the eosinophil count in totally adrenalectomized animals. We can safely conclude that eosinopenia following subcutaneous injection of adrenaline into animals with intact adrenals is due to stimulation of the adrenal cortex. The difference of real opinion is in interpreting how much of the eosinopenic activity is due to indirect stimulation of the adrenal cortex (*via* the pituitary) and how much is due to direct stimulation of the gland. While there is general agreement that adrenaline stimulates the production or release of A.C.T.H., some workers claim that the eosinopenic activity of adrenaline is not entirely due to the release of A.C.T.H. and that adrenaline may directly stimulate the adrenal cortex in hypophysectomized mice.[7,8] Consequently the difficulty of the adrenaline test is in interpreting how much of the eosinopenia is due to direct stimulation and how much is due to indirect stimulation of the adrenal cortex. In this connexion, the dosage of adrenaline may play an important part. Large doses may directly stimulate the gland, while smaller doses fail to do so. Consequently the dose of 0.3 mg. of adrenaline—a small dose—was selected for use in the burned patients in order to reduce or eliminate the direct stimulatory effect of adrenaline and to increase the selectivity of the adrenaline as an indirect stimulator of the adrenal cortex.

The two patients giving abnormal results with adrenaline were considered worthy of report because *repeated* tests failed to produce satisfactory eosinopenia during a phase of mental abnormality, and because later the adrenaline became eosinopenic when the mental condition of the children was returning, or had returned, to normal. Would Dr. Strong and Dr. West not agree that the 12 patients in whom the A.C.T.H. tests gave normal results had more stimulable reserves of the adrenal cortex? Would they not agree that the post-burn phase of eosinopenia which occurs in all patients indicates adrenocortical hyperactivity? The interpretations of the abnormal results in two patients were, I had hoped, critically and cautiously dealt with, giving all the clinical, laboratory, and necropsy evidence for and against adrenocortical failure (Cases 30 and 52). Inactivation of the injected A.C.T.H. may well have been the cause of the abnormal results obtained in Case 52, as there was no other evidence supporting adrenocortical failure.

May I criticize your annotation of my paper (p. 572)? I believe that the main conclusion should be, not "that there is a case for treating some burned patients with cortisone," but that 90% or more of burned patients do not require replacement therapy either with cortisone or A.C.T.H. Finally you state that "patients were found in whom *intravenous* adrenaline was ineffective" (my italics). This is incorrect: adrenaline was used subcutaneously or intramuscularly.—I am, etc.,

SIMON SEVITT.

Birmingham, 15.

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Fructose in Diabetes Mellitus

SIR,—In your annotation (*Journal*, February 27, p. 510) concerning the intravenous administration of fructose, you state that "fructose may prove to be a more useful sugar in conditions where glucose has a time-honoured place—for example, in the treatment of hypoglycaemia." It is the purpose of this letter to draw attention to another hexose sugar that merits study—namely, mannose.

Mannose is slowly absorbed from the gastro-intestinal tract, but if given intravenously there is every evidence that it is well utilized and capable of forming glycogen in the liver and muscles. As long ago as 1924 mannose was shown to be as effective as glucose, and much better than fructose, in preventing the symptoms of insulin hypoglycaemia in experimental animals.[1] Moreover, like fructose but not like glucose, mannose disappears rapidly from the blood stream in the absence of insulin.[2] It is as effective as either glucose or fructose in supporting the respiration of isolated brain tissue.[3] Mannose is as good as glucose, and much better than fructose, in supporting the metabolic turnover of pentosenucleic acid[4] and phospholipid[5] in respiring brain slices. Mannose, like glucose and unlike fructose, can maintain the life of an animal after the removal of the liver[6] and, again like glucose and unlike fructose, can restore to normal the changes in the electro-encephalogram observed during the progressive hypoglycaemia in hepatectomized animals.[7]

The evidence is that insulin is not necessary for the peripheral utilization of either fructose or mannose, but that mannose, possibly because of its greater affinity for the brain phosphorylating enzyme, hexokinase,[8] is much more effective in maintaining cerebral functions. It is to be hoped that in any further trials conducted along the lines suggested in your annotation mannose, as well as fructose, will be investigated.—I am, etc.,

London, Canada. R. J. ROSSITER.

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Congenital Hydrocephalus and Vitamin-A Deficiency

SIR,—Having worked for some years on vitamin-A deficiency,[1] I may perhaps comment on your annotation (*Journal*, April 3, p. 809). Your annotator rightly and cautiously underlines the importance of vitamin-A deficiency in the production of hydrocephalus in all 16 rabbits used in the Cambridge experiment.[2] However, most of the recent experimental work in this field has been carried out on rats. The offspring exhibited in decreasing frequency congenital defects of the eyes, diaphragm, urogenital system, aortic arch, and heart; administration of vitamin A to the deficient mothers at progressively earlier times during pregnancy resulted in a progressive decrease in the rate of malformations.[3] It was therefore surprising to learn[4] that an excessive intake of vitamin A in rats from the second to the sixteenth day of pregnancy causes gross developmental abnormality of the skull with an extrusion of the brain to the external surface of the head as well as more sporadic congenital abnormalities. As the quantity of vitamin A, not only its absence, in the antenatal diet seems to have an important influence on congenital defects, would it not be instructive to repeat the Cambridge experiments with an overdose of vitamin A?—I am, etc.,

London, W.1. Z. A. LEITNER.

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Undescended Testicles

SIR,—Dr. G. I. M. Swyer (*Journal*, April 3, p. 815) attacks Dr. N. S. Craig's letter (*Journal*, March 20, p. 706) as being reminiscent of a mediaeval schoolman because, in support of his opinion that hormone treatment of undescended testicles is futile, he follows the universal practice of scientists and quotes published work. What else is he to do? If Dr. Swyer follows up the references he has been given, he will find he is being referred not to opinion nor to authority, but to questions of verifiable fact, that is to say, of gross anatomy. The best way of stopping this method of treatment would be to get its enthusiasts (preferably accompanied by professors of anatomy) into the operating theatre, and there demonstrate to them the structure of the region they treat, and in particular the misconception on which their treatment depends. In my experience, however, this is impossible: and I would suggest that what is really reminiscent of mediaeval theologians is a refusal to examine the truth of statements which conflict with one's own opinions.

I see two or three cases every week which have been diagnosed as "undescended testicles." Of these some 80% are demonstrably normal, that is to say the testicles can, by those who know how to do it, be brought well into the scrotum. The less anatomical knowledge a practitioner has, the less skill in palpation, and the earlier he tackles these cases, the more "cryptorchids" he will find: there should also be a significant increase during spells of cold weather. Quite a number of these normal cases are sent along for operation because hormones have made no difference in their condition; when left alone the testicles take the normal adult position in their own good time. In my experience hormones are quite unreliable as a means of distinguishing the congenital deformities which need operation from the delayed descent which does not.

Originally hormones were written up as a cure for all varieties of cryptorchidism, and testicles were regularly reported as being brought out of the inguinal canal and the abdomen. In fact I have just received a commercial puff which advises that the testicle should not be brought out of the abdomen too rapidly, in order to give time for the processus vaginalis to close behind it in its flight. One early writer stated that so powerful was the action that he had known the testicle descend twenty minutes after the injection: in default of more exact information of what Dr. Swyer means by curing cases "there and then," I regard this as the record.

However, since I described the retractile testicle, and stated that hormone successes only occurred in this variety,[1] these claims are gradually being abandoned. Now hormones are used to distinguish between ectopic and retractile varieties, on the principle that if the treatment succeeds it is shown to have been unnecessary. I see a number of unilateral cases with one testicle well down in the scrotum which have had hormone treatment, apparently on the notion that in their case the natural substances have been confined to one side of the body. In two seen recently injections had gone on for three and four years respectively before hope and finance failed. As to the psychological aspect, worry about the absence of testes from the scrotum is unknown in the small children whose treatment is being advocated, whereas terror and distress are invariably caused by regularly recurring needle pricks. Worry about non-descent comes on late in development when nearly all cases are in need of surgery; it is curiously rare in any event.

Regarding the claim that in the congenital deformities the cord is lengthened by hormone treatment and facilitates operation, I have never found this effect myself, even after years of injections. I should be grateful for a reference to any exact work on this subject. I do know, however, of some interesting though alarming reports of the effect of hormones on the spermatogenic cells of the rats on whom the original work was founded.—I am, etc.,

London, W.1. DENIS BROWNE.

REFERENCE

1 *Proc. roy. Soc. Med.*, 1949, **42**, 643.

The Sickle-cell Trait and Sickle-cell Anaemia

SIR,—It is unlikely that any one factor by itself will represent the complete answer to the question why a potentially lethal gene can survive at a high incidence. The particular purpose of this letter is to prevent workers in this field from neglecting three approaches :

(1) *The Anthropological Importance of the Sickling Gene.*—The fact that a gene has a selective value and that its frequency may be influenced by known external conditions such as malaria (Allison[1]) does not deter from the fact that knowledge of its distribution will be of value in anthropology. One might as well deny the anthropological value of skin-colour determination on the basis of its being accepted that the pigmentation of a race depends on the climate where this race has been living. All genes exist for one reason or another, and those which we think to be neutral are merely genes of which we have not yet been able to recognize the part they play in evolution. The population of Africa changes rapidly, and tribal barriers may disappear within the next few years. It is hoped that collectors of sickling data will continue to take into account the anthropological classification of the people they investigate.

(2) *The Homozygous→Sickle-cell Anaemia, Heterozygous→Sickle-cell Trait Theory.*—While a very severe sickle-cell anaemia patient will be homozygous for the S gene and a perfectly healthy and normal sickler a heterozygote, there will be a variety of intermediate states. There are factors of which we know yet little (modifiers) which determine the actual quantity of the S haemoglobin in different individuals. Why, for instance, is the proportion of S haemoglobin <50% in S-heterozygotes with normal, and >50% in S-heterozygotes with C haemoglobin ? There are other factors which determine that one sickle-cell anaemia patient suffers more from crises than another with the same haemoglobin level. Dr. Edington[2] has reported that in his experience a sickle-cell anaemia patient may cease having crisis attacks, and I have already commented[3] why I thought that his finding might help in explaining that in some areas a discrepancy exists between the number of sickle-cell disease diagnoses and the calculated incidence of S-homozygotes. In the United States I was impressed by the number of known sickle-cell anaemia patients—adults of both sexes and parents of children who had a persistently lowered haemoglobin level of about 9–11 g.%, but who had otherwise no complaints. Such individuals—presumably homozygotes—are not discovered easily, and to search for them in Africa will require careful surveys. A past history (of crises) which would help in recognizing them is rarely available in Africa. Family studies are often quite impossible and the chemical proof of homozygosity by determining the percentage of S-haemoglobin has only recently come to hand. It is therefore likely that more such people exist in Africa and that they hitherto escaped attention. I believe, in retrospect, that I have seen such individuals in Uganda and for that matter in India. Perhaps some of the cases described by Foy[4] belong to this category. On the other hand, Dr. Edington (*Journal*, April 10, p. 871) is not convinced that sickle-cell crises may not occur in heterozygous individuals. There certainly exists in the United States increasing evidence for yet another condition, a specific intermittent haematuria of sickle-cell trait carriers. No sickle-cell disease patient should be classified as a homozygote unless this has been borne out at least by chemical determination of the haemoglobin composition and if possible also by a family study.

(3) *The Role of Malaria in Maintaining a High Sickling Frequency.*—Edington[2] and for that matter Choremis and his colleagues[5] have both claimed the reverse of Brain's[6] and Allison's[1] suggestion that there was evidence for Raper's[7] tentative proposal that sickling protected against malaria (see also Mackey and Viverelli, *Journal*, January 30, p. 276). They stated that malaria seemed to precipitate sickle-cell crises. It is not necessary to assume that such influence of malaria on sickling conditions should necessarily be disadvantageous. Here again it will be important that one should clearly differentiate between sickle-cell anaemia by itself and the anaemia plus the deleterious crisis, the sickle-cell disease. It is striking that sickle-cell disease is found to be frequent where sickling exists in the absence of malaria or where malaria has recently been eradicated: in the U.S.A., in the Lake Kopais area of Greece, and in the last years in certain townships of Africa. Yet although I was shown many sick infants in the Nilgiri hills in India, where malaria incidence is high, I did not see one with sickle-cell crises. It may be said that areas where malaria has been exterminated are also places where medical services are above average and the diagnosis of sickle-cell crisis will be made more often because of better medical facilities. This can hardly explain why an experienced child specialist should be unable to find at any frequency patients with sickle-cell crises at the most important hospital of Nigeria and yet be able to diagnose the condition in large numbers of people at the University Hospital of Jamaica.[8] If malaria were to have a protective effect against, or a beneficial modifying effect on, sickle-cell anaemia and sickle-cell crisis, this would be another factor helping in sustaining the gene in malarious areas at a higher frequency than one might expect. Sickle-cell crisis where established has such a serious prognosis that the exploration of any possible beneficially modifying agent would be justified.

There will now be a number of investigations such as Dr. Edington's evaluating elsewhere Dr. Allison's findings in East Africa. I would like to plead that an open mind should be kept as to whether malaria could maintain sickle haemoglobin frequency not only by preferentially killing off the non-sickling homozygotes but also by diminishing the disadvantages of the gene in the sickling individuals.—I am, etc.,

London, E.C.1. H. LEHMANN.

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International Nomenclature for ABO Groups

SIR,—Dr. W. Smith (*Journal*, March 13, p. 643) will be interested to know that there is international agreement regarding the nomenclature of the sera used for ABO blood group testing. The World Health Organization set up two international standard sera for ABO blood grouping in 1950[1] ; these are called anti-A and anti-B, and many countries, including the United Kingdom, have similarly named national standards. All sera for ABO grouping issued by the Blood Group Reference Laboratory have been labelled in this way since 1946, and the same nomenclature was in general use in this country throughout the war. The "Minimum Requirements" of the National Institute of Health, Washington, D.C., U.S.A., which corresponds roughly to the Therapeutic Substances Regulations in this country, have used the nomenclature anti-A and anti-B at least since 1946.—I am, etc.,

London, S.W.1. A. E. MOURANT.

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The Longevity of Cambridge Sportsmen

SIR,—Sir Alan Rook in his admirable report (*Journal*, April 3, p. 773) has shown why his conclusions are tentative. It could also be argued that the athletic group on entering the university would reasonably be expected to live longer than the control group if it did not participate in strenuous sport. I do not suggest this was the case and obviously this aspect cannot be tested. The conclusions therefore *must* be tentative.—I am, etc.,

New Barnet, Herts. LL. WYNN JONES.

Osler Memorial Tablet

SIR,—I read the letter from Dr. L. Carlyle Lyon in your columns in 1952[1] about the placing of an Osler Memorial tablet on his old home in Oxford. Visiting Oxford the other day, I looked in vain for a tablet or plaque on the exterior of No. 13, Norham Gardens, commemorative of the fact that the late Sir William Osler, whom it is no exaggeration to describe as "the world's best doctor," lived there during the whole of his tenure of the chair of medicine at the University till his death in December, 1919.

I beg to request the small amount of space required in your columns to bring this matter, for necessary action, to the notice of all who share my view—I feel they must be many.—I am, etc.,

Tilbury. JOHN S. MEIGHAN.

REFERENCE

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Obituary

W. H. S. NICKERSON, V.C., C.B., C.M.G.
M.B., D.P.H.

Major-General W. H. S. Nickerson, who was awarded the Victoria Cross during the South African War, died at his home at Kintyre, Argyllshire, on April 10 at the age of 79.

William Henry Snyder Nickerson was born at New Brunswick, Canada, on March 27, 1875, the son of the Reverend D. Nickerson, who was an Army chaplain. From Portsmouth Grammar School he went on to study medicine at Owens College, Manchester, and graduated M.B., Ch.B. from the Victoria University of Manchester in 1896. Two years later he entered the R.A.M.C. as a lieutenant, and served throughout the war in South Africa from 1899 to 1902, winning the Victoria Cross at Wakkerstroom on April 20, 1900. According to the citation, "Lieutenant Nickerson went, in the most gallant manner, under a heavy rifle and shell fire, to attend a wounded man, dressed his wounds, and remained with him till he had him conveyed to a place of safety."

When war broke out in Europe in 1914 Nickerson, who had by then attained his majority, served with the cavalry in the retreat from Antwerp, and saw further action in the first and second battles of Ypres, at Neuve Chapelle, and on the Somme. Later he served in Salonika. He was mentioned in dispatches six times, promoted to brevet colonel, appointed C.M.G. for his war services in 1916, and C.B. for service in the Black Sea theatre of the war in 1919, in which year he was also awarded the Greek Medal for Military Merit. His promotion was exceptionally rapid all through his Army career, and he was made a major-general at such a young age that when he had served in that rank for the statutory period he was permitted to continue in it for another four years. In 1927 he was appointed Director of Medical Services in India, in succession to the late Sir Walter H. Ogilvie. He was an honorary surgeon to the King from 1925 to 1933, the year he retired. During the last war Major-General Nickerson served variously as a medical officer in an Atlantic convoy, in the Port of London Authority's river emergency service, and in the Home Guard. He married Miss Nan Waller in 1919, and she survives him, together with the son and daughter of the marriage.

Mr. A. E. WYNNE, who died at his home at Margate, Kent, on February 7, was for many years anaesthetist at the Incorporated Dental Hospital of Ireland in Dublin. He was 88 years of age. Albert Edward Wynne was born at Birmingham on September 14, 1865, and had a distinguished career, both academically and on the sports field, at King Edward VI School before he went on to Trinity College, Dublin, to study medicine. He qualified L.A.H. in 1890, taking the Scottish triple qualification in the same year. In 1900 he was elected a Fellow of the Royal College of Surgeons in Ireland, and seven years later he proceeded to the degrees of M.A. and M.D. In Dublin he combined the work of a busy general practice with that of anaesthetist to the Dental Hospital, where he will be long remembered. He continued in practice until his 70th year, when he retired to live at Margate to be near his son, Mr. W. E. C. Wynne, a general surgeon at the Ramsgate and Margate General Hospitals. During the first world war he served as a captain in the R.A.M.C. and acted as assistant surgeon to Drumcondra Hospital. He is survived by his son, Mrs. Wynne having died in 1948.

Dr. CHARLES MELVILLE died on March 25 at the age of 57 after a long illness. Born at Falkirk, he studied medicine at Glasgow University and graduated M.B., Ch.B. in 1920, his studies being interrupted by a period of service in the Army during the first world war. In 1922 he entered general practice at Grangemouth, but managed to continue his studies and took the D.P.H. in 1925. Later he became assistant in the Ear, Nose, and Throat Department of Falkirk Royal Infirmary, and on the retirement of his chief, Dr. George B. Brand, took over full charge of the department. He carried on this work in addition to that of his general practice until the advent of the National Health Service, when he resigned from his practice to devote himself to consultant work. In 1951 the onset of a vascular lesion forced him to give up all active work.

Dr. G. M. FERGUSON writes: Dr. Melville was one of the most widely known and respected members of the profession in central Scotland. As a busy general practitioner for 26 years in Grangemouth, he gained the confidence and affection of his patients for his continuous devotion to their interests, and later as a consultant he merited and obtained the gratitude and trust of his colleagues. He took a leading and energetic part in the affairs of the B.M.A. during most of his career. His work for its charities and as a member of a number of its committees, and his services as chairman of the local panel committee, were recognized in 1948 by a presentation from his colleagues. In the same year he was elected vice-chairman of the executive council, a post which he held until his illness. He was honorary secretary of the Stirling Branch of the B.M.A. from 1927 to 1932 and president of the Branch in 1934–5. He also represented his constituency at eleven Representative Meetings from 1937 to 1948. Dr. Melville was also well known in the world of cricket, captaining both his university and county teams in his younger days and playing for Scotland against the Australians on one occasion. In addition he was an expert angler and deeply interested himself in his later years in the study of bird life. In spite of all these activities, his main interest was always centred in his work, and even during his last illness his greatest desire was to be allowed to continue that work. He had a strong sense of duty, and was a loyal colleague and a trusted friend, unsparing of his own time and health in the service of his patients. His loss will be widely mourned. He is survived by his wife and daughter, both medical graduates, and a son, to all of whom deep sympathy is extended.

Medico-Legal

VICARIOUS RESPONSIBILITY OF HOSPITAL AUTHORITIES

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

The vexed question of the vicarious responsibility of hospital authorities for the negligence of various members of the hospital staff was once more canvassed in the Court of Appeal in the case of *Roe and Woolley* v. *Minister of Health*,[1] although the appeal was dismissed on grounds which involved no decision upon it.

At the trial Mr. Justice McNair had decided that, if Dr. Graham had been negligent—though in fact the judge found he had not been—the hospital authority would not have been vicariously liable for his negligence. Dr. Graham's position was that he was visiting anaesthetist to the hospital, paid from a fund set aside for the purpose from the hospital funds, and under an obligation with another doctor to provide regular anaesthetic services. Mr. Justice McNair considered that his position was equivalent to that of "consulting physicians and surgeons," and based his decision that the hospital authority as employer was not responsible if Dr. Graham had been negligent on the judgments of Lord Greene in *Gold* v. *Essex C.C.*[2] and of

Lord Justice Somervell and Lord Justice Morris in *Cassidy* v. *Ministry of Health*.[3 4] He impliedly rejected the judgment in Cassidy's case of Lord Justice Denning, which was based upon broader grounds than those of Lords Justices Somervell and Morris. Lord Justice Denning had decided that, since the hospital authority is under a duty of care towards the patient, it cannot escape liability by delegating the performance of the duty to a consultant employed under a "contract for services" any more than by delegating it to a house-surgeon employed under a "contract of service."

In his judgment in the Court of Appeal in Roe and Woolley's case Lord Justice Somervell decided that Mr. Justice McNair had been wrong in holding that Dr. Graham was in a position similar to a consultant. In his view the anaesthetists were in the same position as the house-surgeon in Cassidy's case. The Lord Justice did not deal with the matter on the wider ground on which Lord Justice Denning had based his judgment in Cassidy's case. Lord Justice Denning, consistently with his previous judgment in Cassidy's case, held that Mr. Justice McNair was wrong because the hospital authority was vicariously responsible for the negligence of the whole of its staff. Lord Justice Somervell added that the position of hospitals in this respect under the National Health Service Act might be different from that of voluntary or municipal hospitals and would have to be decided when it arose.

By the decision of this appeal the law in England is left where it was left by Cassidy's case, and it remains to be seen whether, if the hospital authority's vicarious responsibility for consultants were litigated to the House of Lords, the House would adopt the wider principle as exemplified in the judgments of Lord Justice Denning.

The law as applied in Scotland is the very reverse, and is still based on Lord President Clyde's judgment in *Reidford* v. *Magistrates of Aberdeen* in 1933, that—

> "All the managers undertake is to provide an efficient, heated, clean, wholesome sick-house, equipped with the necessary furniture and fittings for the reception of patients; to employ a competent staff; and to provide the necessary medicine and food. But they do not, as I understand any conceivable view of their functions, undertake to treat or to dose or to operate upon any of those who come into their institution."

This sturdy view is broadly the same as had been taken in Hillyer's case[5] in England. Although attractive, it leads to the sort of logical difficulties expressed by Lord Goddard in Gold's case, where he said: "I cannot understand on what principle a hospital authority is to be exempt from liability if a nurse carelessly administers a dose of poison to a patient instead of medicine, and yet is liable if the cook mixes some deleterious substance in the patient's food."

Although in many fields the law of England and the law of Scotland are wholly different, negligence is not in theory one of those fields. It is evidently high time some gallant litigant on one side of the Border or the other appealed to the House of Lords to give that august tribunal the opportunity to resolve the conflict.

REFERENCES

1 *British Medical Journal*, April 17, 1954, p. 940.
2 [1942], 2 K.B. 293.
3 [1951], 2 K.B. 343.
4 *British Medical Journal*, March 3, 1951, p. 480.
5 [1909], 2 K.B. 820.

The Services

Major-General A. G. Harsant, C.B., O.B.E., late R.A.M.C., has relinquished his appointment as Director of Surgery and Consulting Surgeon to the Army.

Lieutenant-Colonel J. D. Galloway, R.C.A.M.C., has been appointed O.B.E. (Military Division) in recognition of gallant and distinguished services in Korea.

Colonel F. R. Langmaid, O.B.E., T.D., R.A.M.C., T.A., has been appointed Honorary Physician to the Queen in succession to Colonel F. R. Sandford, C.B.E., M.C., T.D., who has been transferred to the T.A.R.O.

Medical Notes in Parliament

Welfare Foods

Sir GUY LLOYD (Renfrew, East, Con.) asked the Minister of Food what were the proportions of welfare foods available through his department for children and expectant mothers that were being taken up. Major LLOYD GEORGE stated on April 12 that about 97% of those entitled to obtain milk or national dried milk under the welfare foods service did so. The quantities of the vitamin supplements taken up in 1953 expressed as a proportion of the full entitlement were as follows: orange juice 29.4%; cod-liver oil 23.8%; vitamin tablets 32.6%. The percentage of persons who obtained the vitamin supplements was higher than these figures suggested, because many did not take up their full entitlement.

Clean Food Rules

Lieut.-Col. M. LIPTON (Brixton, Lab.) asked the Minister of Food on April 14 what representations he had received from the National Caterers' Federation relating to the Food and Drugs (Amendment) Bill, and what reply he had sent. Dr. CHARLES HILL, the Parliamentary Secretary, said that the department received a letter and memorandum from the Federation on March 16 expressing certain views about the new legislation and suggesting further consultation with trade interests about the form of public food hygiene regulations. They attended a conference on April 5 and made a number of points, which would be carefully considered.

Iodized Salt

Mr. J. B. HYND (Sheffield, Attercliffe, Lab.) asked the Minister of Food whether he had considered, in connexion with the proposed legislation for the compulsory use of iodized salt, the number of people who were allergic to iodine, and whether he would give the House assurances on their behalf. Dr. CHARLES HILL, the Parliamentary Secretary, replied on April 14 that no decision had yet been taken to add iodine to salt. Before any such decision was taken full consideration would be given to the point raised.

Tuberculosis Among Kikuyu

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Secretary of State for the Colonies on April 14 what percentage of Kikuyu prisoners were suffering from tuberculosis, and what precautions were being taken to prevent the spread of this disease among the prisoners. Mr. H. L. HOPKINSON, the Minister of State, said that he would obtain the figure from Kenya. The following precautions were taken against the spread of the disease: regular inspection by medical officers of hygiene conditions in all prisons; medical examination of all convicts on admission to prison; special diets and medicine for all convicts in low physical condition; isolation of all tuberculosis suspects; and evacuation of all infected cases to tuberculosis wards in the prison hospital in Nairobi.

Diphtheria Inoculations in Scotland

Mr. JAMES STUART, Secretary of State for Scotland, supplied Mr. S. P. VIANT (Willesden, West, Lab.) with figures showing the estimated percentages of children under 15 years and under 5 years of age in each Scottish county who had been inoculated against diphtheria. Those under 15 ranged from 96% in Peebles to 45% in Orkney, and those under 5 from 99% in Midlothian to 34% in Orkney.

Cancer Experiments on Mice

Sir DAVID MAXWELL FYFE, Home Secretary, informed Mr. PETER FREEMAN (Newport, Lab.) on April 15 that since 1907, when records were first kept, to the end of 1952, a total of 1,367,820 experiments had been made on animals—almost all of them on mice—for cancer research. He gave the list of annual totals, which (apart from war years) varied

between 8,083 in 1924 to 95,991 in 1952. In the early years 1907–11 the numbers were between 40,000 and 49,000, then fell to 24,000 and continued falling until 1928, spurted to 43,000 and 50,000 in 1933 and 1934, fell again until 1947, and since 1948 have been 56,585, 75,343, 78,192, 91,410, and 95,991 respectively.

Dental Technicians

Mr. R. E. WINTERBOTTOM (Sheffield, Brightside, Lab.) drew attention on April 15 to unemployment among dental technicians, and the loss of highly skilled craftsmen to the Health Service, which he attributed to the cuts in the Service.

Miss PAT HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, disputed this, and suggested that the cause was that there had been too many entrants. In 1950, owing to the immediate and high demand, 5,000,000 dentures were supplied under the Health Service. Even without the imposition of the charges for dental treatment the level of 5,000,000 could not possibly have been maintained. In 1953 the number of dentures supplied was 2,000,000, and she thought this figure would represent the average annual demand for some years, and she hoped that it would gradually get less as the effect of greater emphasis on conservation work became apparent.

Myxomatosis Outbreaks

Mr. G. R. H. NUGENT, Parliamentary Secretary, Ministry of Agriculture, informed Mr. A. HURD (Newbury, Con.) on April 15 that there were 17 established centres of myxomatosis infection among rabbits, five of which had been confirmed in the past month. The Minister would report from time to time on the spread of the disease into new areas, but weekly statements for which Mr. Hurd had asked did not seem justified at present. The advisory committee would continue to watch closely the extent and character of the outbreaks.

Coroners Bill.—The Coroners Bill was given a third reading in the House of Commons on April 9 and has been sent to the House of Lords.

Universities and Colleges

UNIVERSITY OF OXFORD

The following elections are announced: To the War Memorial Medical Scholarship at University College, I. G. McGill (Bablake School, Coventry); to a Nuffield Scholarship in Medicine at Pembroke College, D. C. E. Speller (Caterham School); to a Nuffield Medical Scholarship at Worcester College, W. R. A. Muntz (Oundle School); to a Nuffield Scholarship in Medicine at Somerville College, S. N. Clayton (St. Felix, Southwold): to an Exhibition in Medicine at St. Hugh's College, G. M. Roberts (North London Collegiate School).

UNIVERSITY OF LONDON

The following candidates have been approved at the examinations indicated:

ACADEMIC POSTGRADUATE DIPLOMA IN MEDICAL RADIOLOGY (DIAGNOSIS).—P. L. Brangwin, Edwina R. Goodall.

ACADEMIC POSTGRADUATE CERTIFICATE IN PUBLIC HEALTH.—*London School of Hygiene and Tropical Medicine:* G. A. Ademola, Doreen P. Allan, N. K. Bharucha, D. W. Boatman, S. C. Bose, H. H. S. Brown, J. Chatterjee, H. J. S. Coldham, C. P. Collins, L. P. Darmanin, C. B. Drew, Y. G. Farran, E. R. Gauld, G. S. Godiwalla, G. McL. Gorrie, Catriona M. Gourlay, A. Grut, K. L. Gupta, T. B. Harrison, M. A. Heasman, F. M. James, H. James, B. Lall, R. J. Lande, I. Laufer, W. S. Millar, S. L. Morrison, B. J. Ll. Moss, H.-H. Mueller, K. W. Newell, Joycelyn H. W. Newman, R. G. Nichols, S. Ogen, T. A. Plumley, D. W. Quantrill, C. J. Radway, D. H. Shennan, Rachel E. W. Sillett, C. Slome, C. I. Somaya, R. J. K. Tallack, Pin Hui Teng, A. E. P. Twort, K. L. Vasa, R. B. Walker, F. A. Wickremasinghe, F. Zangen.

ACADEMIC POSTGRADUATE CERTIFICATE IN TROPICAL MEDICINE AND HYGIENE.—*London School of Hygiene and Tropical Medicine:* L. Noronha.

J. M. Ledingham, M.D., M.R.C.P., Lecturer in Medicine at the London Hospital Medical College, has been appointed to the University Readership in Medicine tenable at that College.

The following candidates have been approved at the examinations indicated:

M.D.—*Part I:* C. P. T. Alexander, J. A. S. Amos, P. B. Cook, P. W. Darby, Katharine M. Dormandy, J. H. Evans, J. T. Groves, C. P. Handforth, P. M. Higgins, Margaret A. Holroyde, E. T. Hughes, A. R. Kagan, C. S. Livingstone, Eunice Lockey, C. J. Luças, R. P. Michael, G. R. J. Moodie, R. Moore, J. D. Pollit, F. C. Rose, A. L. Slater, C. K. M. Thacker.

M.S.—*Part I:* P. J. W. Monks.

Professor Charles Singer has been appointed to represent the University at the XIVth International Congress of History of Medicine, to be held at Rome and Salerno from September 13 to 20, 1954.

Professor J. M. Mackintosh has been re-nominated for appointment as a representative of the University on the governing body of the London School of Economics and Political Science.

The following have been appointed representatives of the University on the committees of management of the federated and associated institutes of the British Postgraduate Medical Federation, indicated in parentheses, for the three years ending December 31, 1956: Dr. C. F. Harris and Dame Lillian Penson (Institute of Basic Medical Sciences); Mr. W. P. Cleland (Institute of Cardiology); Professor W. E. Herbert (Institute of Dental Surgery); Sir Archibald Gray (Institute of Dermatology); Dr. E. Bonham Carter (Institute of Diseases of the Chest); Mr. V. E. Negus (Institute of Laryngology and Otology); Professor R. W. Russell (Institute of Neurology); Professor W. C. W. Nixon (Institute of Obstetrics and Gynaecology); Professor J. Z. Young, F.R.S. (Institute of Orthopaedics); Professor F. R. Winton (Institute of Psychiatry); Mr. D. F. Ellison Nash (Institute of Urology).

Professor J. E. Roberts and Professor J. Whillis will be the representatives of the Board of Pre-clinical Studies on the Board of Advanced Medical Studies for 1954.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *London Hospital Medical College,* Mr. Geoffrey Flavell (Surgery). *Charing Cross Hospital Medical School,* Dr. H. I. Winner (Pathology); Dr. J. B. E. Baker (Pharmacology). *University College,* Dr. M. de B. Daly (Physiology). *Guy's Hospital Medical School,* Dr. J. A. Nissim (Pharmacology).

Mr. J. B. Kinmonth has been appointed a representative of the Board of Advanced Medical Studies on the Special Advisory Board in Veterinary Medicine, in place of Sir James Paterson Ross, who has resigned.

The following have been recognized as teachers of the University in the subjects indicated in parentheses: *St. George's Hospital Medical School,* Dr. J. A. Dudgeon (Pathology). *Institute of Psychiatry,* Dr. A. D. Leigh, Dr. D. A. Pond, Dr. P. D. Scott, and Dr. F. K. Taylor (Psychiatry). *University College Hospital Medical School,* Dr. E. N. Rowlands (Medicine).

UNIVERSITY OF EDINBURGH

At a Graduation Ceremonial held on December 18, 1953, the following degrees and diplomas were conferred:

M.D.—[1]R. C. Humphreys, [2]J. D. Kerr, [2]T. W. Lees, [1]R. G. Mitchell, [1]C. F. Rolland.

CH.M.—[1]A. I. S. Macpherson.

PH.D.—*In the Faculty of Medicine:* W. St. C. Bauld, D. S. Chowdhary, M. Ishaq. *In the Faculty of Science:* A. B. Monro.

M.B., CH.B.—A. McI. Anderson, B. R. Bayne, A. T. Burnet, G. Gilray, I. B. Grant, Christine F. Hannah, J. L. Leadbitter, W. D. W. Miller, Jadwiga M. Weyndling.

DIPLOMA IN MEDICAL RADIODIAGNOSIS.—G. M. Ashurst, A. A. Donaldson, H. Gardner, H. Levon, Margaret C. Macleod, A. M. Stewart.

DIPLOMA IN MEDICAL RADIOTHERAPY.—N. R. Mackay, J. McLelland, J. Newall, J. G. Pearson.

The following scholarships, etc., in the Faculty of Medicine were awarded: *Wilkie Surgical Research Scholarship,* H. A. F. Dudley. *Andrew Graham Ritchie Bursaries,* C. J. W. Huston and Rosemary McCredie. *Mackie Bursaries,* J. B. Rae and J. T. Wilson. *E. B. Jamieson Prizes in Anatomy,* Joan E. G. Caves, I. D. Heath, C. J. W. Huston, Joan L. Young. *Russell-Crighton Prize,* D. Dow.

[1]Highly commended for thesis. [2]Commended for thesis. [3]*In absentia.*

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH

At the annual meeting of the College held on December 3, 1953, Dr. L. S. P. Davidson was elected President, Dr. Ian G. W. Hill, C.B.E., T.D., was elected Vice-President, and the following were elected Members of Council: Dr. Edward R. C. Walker, Dr. W.

Lindsay Lamb, Dr. I. Simson Hall, Dr. R. M. Murray-Lyon, and Dr. Thomas Anderson. Dr. J. Halliday Croom was reappointed Secretary, and Dr. J. Alastair Bruce was reappointed Treasurer.

At a quarterly meeting of the College held on February 2, with the President, Professor L. S. P. Davidson, in the chair, the following were elected Members of the College: J. H. Bowie, B. Ghosh, M. E. Mahdi, S. S. Manchanda, J. C. Simson, C. W. Marsden, J. B. Mackay, K. P. N. Pai, K. Parameswaran, H. Klevansky, G. Larkins, S. N. Sengupta, W. B. Muston, A. Hordern, M. K. El Shawarby, I. C. Brannen, N. Radhakrishnan, J. A. Clark, J. Hampson, C. R. R. Pillay, S. A. R. Ali, V. P. Datta, M. H. M. Gaber, P. N. Mathur, R. G. Willison.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At a meeting of the College held on December 16, 1953, with Professor Walter Mercer, President, in the chair, the following were admitted Fellows after having passed the requisite examinations: S. Ansari, G. O. Clark, A. K. Das, R. A. Daws, D. C. D'Netto, F. H. Gamali, A. Ghani, P. Goldstein, I. M. Grant, W. McI. S. Ironside, F. D. Johnston, R. N. Katariya, G. Kerridge, P. Kilburn, J. S. Lekias, I. Opeskin, M. G. Pearson, M. Q. K. Raja, J. R. Salas, G. R. T. Serpell, R. P. Sharma, P. R. Shroff, A. M. Shukri, E. H. J. Smyth, M. J. Twohig, W. B. Young.

Vital Statistics

Some Vital Statistics of 1953

The estimated home population of England and Wales at December 31, 1953, was 44,166,000 (21,249,000 males, 22,917,000 females).[1] This is an increase of about 420,000 since the 1951 census. Projections of the population show that, on certain assumptions, the total population will increase to 45,378,000 in 1963, 46,175,000 in 1973, and 46,617,000 in 1983, declining to 46,382,000 in 1993. On the basis of the death rates for the year 1952 the expectation of life of a boy at birth is 67.06 years and of a girl 72.35. This compares with 48.53 and 52.38 respectively on the basis of the death rates for the years 1901–10.

Deaths from accidental poisoning rose, reaching 659 in the first three quarters of 1953 compared with 586 during the corresponding nine months of 1952, while deaths from accidental burns dropped from 593 to 522. The number of suicides increased in the same period from 3,299 to 3,541.

In the December quarter the death rate per 1,000 population in Greater London was 9.8. This compared with 10.1 in New York and Copenhagen, 9.0 in Stockholm, 8.7 in Oslo, and 8.2 in Rome. A comparison of death rates of children under 1 year of age in September quarter, 1953, shows that the England and Wales rate of 22 per 1,000 related live births compared with Netherlands 19, Australia 25, U.S.A. 26, Scotland 28, France 33, and Italy 64.

Venereal Diseases

In England and Wales during the quarter ending September 30, 1953, 1,446 new cases of syphilis were reported as attending the clinics. Of these, 256 were classified as primary, secondary, or latent in first year of infection. 23 cases of congenital syphilis in children aged under 1 year were reported, and 172 cases in people over that age. New cases of gonorrhoea numbered 5,588, of chancroid 84, and of non-gonococcal urethritis (males only) 3,682.

Northern Ireland in 1952

Live births numbered 28,760 in Northern Ireland in 1952, giving a rate of 20.9 per 1,000 population. This was 0.2 above that for 1951 but 0.8 below the average rate for 1947–51. The infant mortality rate was 39 per 1,000 live births, the lowest so far recorded in Northern Ireland. The total number of deaths registered was 14,812, giving a rate of 10.8 per 1,000 population. This was 2.0 below the rate for 1951, and 1.1 below the average rate for 1947–51. The death rate from tuberculosis continued to fall, being 0.3 per 1,000 population as compared with the average rate of 0.39 for 1947–51.

[1] *Registrar-General's Quarterly Return* No. 420. H.M.S.O., 2s.

England and Wales in First Quarter

The incidence of infectious diseases was generally below the average of the first quarter, the only exceptions being dysentery and enteric fever. The number of notifications of dysentery has steadily increased throughout the quarter from 322 in the first week to 1,642 in the thirteenth. The high level of enteric fever was due to the recent outbreak of paratyphoid fever in South Wales; 170 of the 244 cases of enteric fever were notified in Wales. The fall in the number of notifications of diphtheria was quite small, and it seems that an irreducible hard core of infection is being reached.

A comparison of the number of notifications for the last five first quarters is given below:

Disease	1950	1951	1952	1953	1954
Scarlet fever	24,802	12,088	18,013	20,550	15,868
Whooping-cough	23,619	66,865	35,042	34,207	28,985
Diphtheria	955	572	456	264	246
Measles	54,568	311,709	64,596	350,836	23,340
Acute pneumonia	13,720	26,536	12,960	20,005	10,507
Meningococcal infections	536	662	562	595	515
Acute poliomyelitis	512	339	288	345	332
Dysentery	3,938	13,995	6,936	4,449	10,808
Enteric fever	154	149	126	123	244

Infectious Diseases

The largest fluctuations in the trends of the notifications of infectious diseases in England and Wales during the week ending April 3 were increases of 327 for dysentery, from 1,315 to 1,642, and 263 for measles, from 2,067 to 2,330, and a decrease of 132 for acute pneumonia, from 661 to 529.

The largest increases in the notifications of measles were 91 in Cumberland, from 58 to 149, and 90 in Lancashire, from 339 to 429, and the largest decrease was 56 in Staffordshire, from 264 to 208. 1,474 cases of scarlet fever, 18 fewer than in the preceding week, were notified, and only small fluctuations were reported in the local trends. The number of notifications of whooping-cough were 2,546, being 7 fewer than in the preceding week, and the only large variation in the returns was an increase of 59 in Yorkshire West Riding, from 143 to 202. 22 cases of diphtheria were notified, being 8 more than in the preceding week. The chief features of the returns for diphtheria were a rise in Lancashire from 3 to 6 and in Durham from 0 to 3.

The number of notifications of paratyphoid fever declined from 20 to 11 and in Wales from 17 to 7. The chief centre of infection was Glamorganshire 5 (Cardiff C.B. 4).

21 cases of acute poliomyelitis were notified. These were 1 fewer for paralytic and 2 fewer for non-paralytic than in the preceding week. The largest returns were Warwickshire 4 (Birmingham C.B. 3), Somersetshire 3, and Nottinghamshire 3 (Beeston and Stapleford U.D. 2).

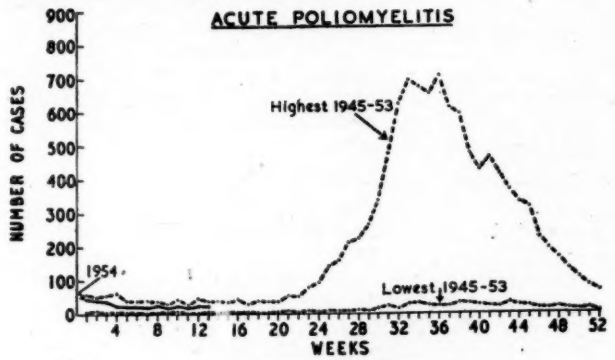
The notifications of dysentery were the largest since this disease was made notifiable in 1919, except for the week ending March 17, 1951, when 1,672 cases were notified, 30 more than in the week reviewed here. The largest returns were London 266 (Islington 84, Lewisham 36, Chelsea 29, Hackney 19, Hampstead 12, Shoreditch 10), Lancashire 226 (Salford C.B. 57, Bolton C.B. 30, Manchester C.B. 20, Eccles M.B. 20, Preston C.B. 13, Liverpool C.B. 10, Worsley U.D. 10), Yorkshire West Riding 198 (Brighouse M.B. 47, Bradford C.B. 26, Leeds C.B. 26, Hebden Royal U.D. 22, Dewsbury C.B. 21, Sheffield C.B. 19, Keighley M.B. 13), Leicestershire 121 (Leicester C.B. 115), Middlesex 107 (Hornsey M.B. 28, Southall M.B. 18, Willesden M.B. 18, Ealing M.B. 10), Carmarthenshire 86 (Carmarthen M.B. 81), Berkshire 78 (Maidenhead M.B. 69), Essex 64 (West Ham C.B. 16, Walthamstow M.B. 12), Norfolk 52 (Norwich C.B. 51), Surrey 47 (Epsom and Ewell M.B. 37), Kent 45 (Margate M.B. 28), Warwickshire 45 (Birmingham C.B. 35), Oxfordshire 41 (Oxford C.B. 36), Devonshire 40 (Exeter C.B. 34).

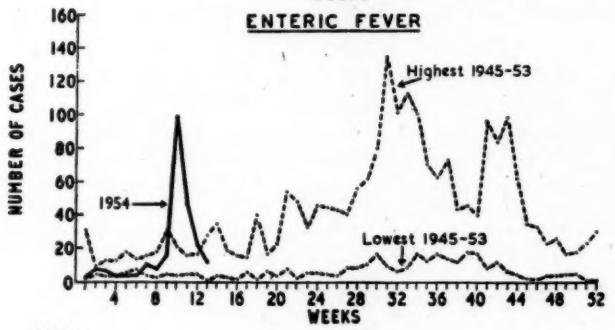
Staffordshire 37 (Cannock U.D. 20), Cheshire 30 (Ellesmere Port U.D. 29), Sussex 23 (Hove M.B. 13), and Gloucestershire 20 (Bristol C.B. 12).

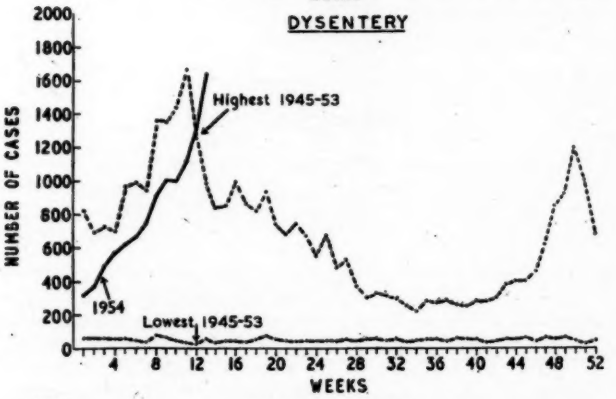
In Scotland dysentery reached a new high level with 438 notifications. The largest returns were 235 in Glasgow, 89 in Lanark county, 42 in Edinburgh, and 35 in Dundee.

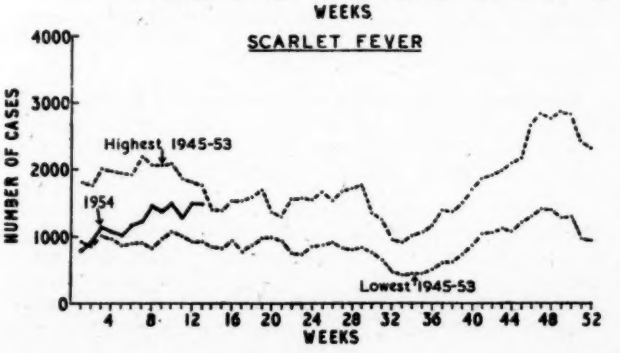
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 3** (No. 13) and corresponding week 1953.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire
Diphtheria	22	1	11	1	1	11	1	6	1	
Dysentery	1,642	266	438	3	5	423	60	89	2	
Encephalitis, acute	6	0				10	0	0	0	
Enteric fever:										
Typhoid	1	0	4	0	1	6	0	1	0	4
Paratyphoid	11	2	1	1	0	7	1	0	0	
Food-poisoning	178	18		0		63	14		1	
Infective enteritis or diarrhoea under 2 years				7	26				11	7
Measles*	2,330	45	161	55	498	21,166	953	401	208	232
Meningococcal infection	39	5	17	2	2	43	6	14	0	2
Ophthalmia neonatorum	30	5	5	0		36	4	9	0	
Pneumonia†	529	29	250	12	2	937	72	290	22	6
Poliomyelitis, acute:										
Paralytic	14	0	2	1		31	2	0	0	
Non-paralytic	7	0				7	1			
Puerperal fever§	245	42	16	0		221	27	11	0	1
Scarlet fever	1,474	76	153	40	43	1,403	96	146	40	38
Tuberculosis:										
Respiratory	777	85	144	34				135	42	
Non-respiratory	103	7	19	5				29	2	
Whooping-cough	2,546	105	400	45	42	2,508	148	273	31	76

DEATHS in Great Towns	1954 Eng. & Wales	1954 Lond.	1954 Scot.	1954 N. Ire.	1954 Eire	1953 Eng. & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire
Diphtheria	0	0	0	0	0	0	0	0		0
Dysentery	0	0		0		0	0			
Encephalitis, acute			0		0		0			0
Enteric fever	0	0	0	0		0	0	0		
Infective enteritis or diarrhoea under 2 years	11	1	0	2	0	9	1	1	3	1
Influenza	6	1	0	0	0	52	7	7	3	1
Measles			0	0	1		0	0		0
Meningococcal infection			0	0			2	0		
Pneumonia	235	28	25	9	7	267	32	25	12	9
Poliomyelitis, acute	0	0			0	4	1			0
Scarlet fever			0	0	0		0	0		0
Tuberculosis:										
Respiratory	99	10	6	5	8	115	20	15	4	11
Non-respiratory			2	0	0		3	0	0	2
Whooping-cough	2	0	1	0	0	7	1	0	0	2
Deaths 0–1 year	212	17	26	8	30	226	28	26	15	18
Deaths (excluding stillbirths)	5,438	720	721	125	211	5,587	775	599	144	159
LIVE BIRTHS	8,231	1227	982	217	448	7,185	1009	925	231	379
STILLBIRTHS	218	23	26			199	28	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Holiday Exchanges Abroad.—The International Medical Visitors' Bureau of the British Medical Association is able to assist doctors in Britain, through the medical associations of the countries on the Continent, to find medical families on the Continent interested in arranging holiday exchanges for their children, *au pair* visits for older children, or occasionally exchange of houses. Last year more than 50 families (Continental and United Kingdom) are known to have made satisfactory exchange arrangements. Notices about exchange hospitality wanted by Continental doctors are published from time to time under "Notes and News" in the *Supplement*. Anyone interested in this scheme should write, giving full details, such as children's ages, when and where they would like to go, what facilities are offered in this country, etc., to Brigadier H. A. Sandiford, Medical Director, International Medical Visitors' Bureau, B.M.A. House, Tavistock Square, London, W.C.1.

Residential Unit for Psychotic and Maladjusted Children.—In every area there are some children who are so mentally disturbed that they cannot attend any recognized school, or benefit by treatment in child guidance clinics or hospital psychiatric departments. To meet their need the North-west Metropolitan Regional Hospital Board has established a small residential unit in a large country house, "High Wick," near St. Albans. The unit aims to provide a stable, friendly environment and the necessary psychotherapy for about 20 psychotic and maladjusted children aged between 3 and 10 years. It will be staffed by a matron, a teacher, and house mothers, each of whom will endeavour to establish and maintain a continuous relationship with the individual children. The Mid-Herts Group Management Committee, which is responsible for the unit, regards it as experimental in nature, and its development will be guided by experience of its working. The unit opened officially on April 23.

Royal College of Surgeons of England.—On April 18 the council met for the last time in the old Council Room of the College which has been used for these meetings for over 100 years. The next meeting will be in the new room in the rebuilt College. The honorary Fellowship was conferred on Dr. G. Gavin Miller, of Montreal, and the following were admitted to the Fellowship without examination as medical practitioners of at least 20 years' standing: Mr. J. W. H. Grice (Tunbridge Wells), Mr. D. M. E. Thomas (Sully, Glamorgan), Professor G. Hadfield (London), Professor J. Trueta (Oxford), and Mrs. D. R. Campbell (Coventry). Others admitted to the Fellowship were Mr. W. A. Jackman (Bristol) and Mr. R. R. Simpson (Hull). Dr. W. D. Paton, reader in pharmacology and therapeutics at University College Hospital Medical School, London, was admitted as the first professor of pharmacology at the College.

British Cardiac Society.—The thirty-third annual general meeting of the British Cardiac Society was held at Downing College, Cambridge, on April 9 under the chairmanship of Dr. Leslie Cole. Both the morning and afternoon sessions were devoted to short communications, and included papers on the pathological lesion in endomyocardial fibrosis, baroceptor responses in acute rhythm change, the diagnosis of mitral incompetence by cardiac catheterization, a review of 30 cases of isolated pulmonary stenosis, valvotomy for both acquired and congenital aortic stenosis, and the action of hexamethonium bromide on the pulmonary circulation in mitral stenosis. A dinner was held in college.

Conference on Industrial Atmospheric Pollution.—The British Occupational Hygiene Society held a conference on April 6 at the London School of Hygiene and Tropical Medicine to discuss problems of atmospheric contamination in industry. In his opening address, Professor E. J. King, the president, thanked Dr. Thomas Bedford, on behalf of members, for his work in founding the Society and for leading it through its first year of life. He also welcomed visitors from overseas. The papers presented at the conference were "The Investigation and Control of Atmospheric Contaminants in Factories," by Drs. M. W. Goldblatt and J. C. Gage, of the Industrial Hygiene Laboratories, I.C.I., Ltd.; "The Measurement of Dust Exposure," by Dr. B. M. Wright, of the Medical Research Council's Pneumoconiosis Research Unit; and "Permissible Levels of Exposure to Ionizing Radiations and Radioactive Materials," by Dr. W. G. Marley, of the Atomic Energy Research Establishment, Harwell. The conference was attended by 150 members and visitors. Copies of the proceedings will be available from the Hon. Secretary, Mr. Peter C. G. Isaac, Public Health Engineering Laboratory, King's College, Newcastle-upon-Tyne.

Jacksonian Prize.—The 1953 prize was awarded by the council of the Royal College of Surgeons to Mr. J. H. Peacock, lecturer in surgery at Bristol, for his essay on "Pathology and Surgery of Peripheral Vascular Occlusion." The subject for the 1955 Jacksonian prize essay will be "Diaphragmatic Hernia."

Metropolitan Regional Board's Clinical Prizes.—Last year we announced that the South-west Regional Hospital Board was offering up to nine £100 research prizes during 1953 (*Journal*, January 31, 1953, p. 283). A similar competition is being held this year. The winners in last year's competition were:—*Consultants and S.H.M.O.s*: Dr. M. Hamilton, Dr. A. M. Read, and Dr. D. A. J. Williamson; *Senior Registrars and Registrars*: Mr. G. Bennett, Dr. G. S. Crockett, and Dr. C. Donovan; *House Officers*: Mr. A. O. Wilson and Mr. M. Wynyard.

Sir Russell Brain, P.R.C.P., has been elected an honorary Fellow of the American College of Physicians.

Irish Honorary Degrees.—On April 8 the honorary degree of LL.D. of the National University of Ireland was conferred on Dr. E. P. Carey, president of the Graduates Club of the N.U.I. in London for six years, and on Dr. P. P. Lynch, a member of the Dental Council and the Medical Research Council of New Zealand.

Professor G. I. Strachan, professor of obstetrics and gynaecology in the Welsh National School of Medicine, is to receive the honorary degree of LL.D., Glasgow University, at a ceremony on June 16.

COMING EVENTS

Renal Association.—The annual general meeting will be held at the Ciba Foundation, 41, Portland Place, London, W.1, on April 28 at 4.30 p.m., *not* on May 28 as stated in our issue of April 17, p. 943.

Hunterian Society.—The annual general meeting will be held at the Talbot Restaurant, London Wall, E.C.2, on April 26 at about 8.30 p.m. It will be preceded by the fourth dinner meeting at 7 for 7.30 p.m. An address will be given by Mr. W. R. Le Fanu, librarian of the Royal College of Surgeons, on "The Hunter–Baillie Manuscripts." Further information from Mr. R. S. Murley, 95, Harley Street, London, W.1.

Contraceptive Technique.—A lecture and demonstration will be given by Dr. Marie Stopes, Ph.D., at the Mothers' Clinic, 108, Whitfield Street, London, W., on May 6 at 2.30 p.m. Tickets must be obtained in advance.

Christian Medical Fellowship.—A week-end house party will be held at the Belsfield Hotel, Windermere, from May 7 to 10, and a week-end conference at the Linden Hall Hydro, Bournemouth, from May 21 to 24. Details are obtainable from the secretary of the Fellowship, 39, Bedford Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, April 26

ASSOCIATION OF PSYCHIATRISTS: SOUTH-WEST METROPOLITAN REGION.—At B.M.A. House, 5.30 p.m., general meeting.

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 64, London Wall, E.C., 7 for 7.30 p.m., annual general (dinner) meeting. Mr. W. R. Le Fanu: Hunter-Baillie MSS. in the Library of the Royal College of Surgeons.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: The Hypermetropic Patient. Astigmatism. Bifocals.

Tuesday, April 27

ROYAL STATISTICAL SOCIETY: STUDY CIRCLE ON MEDICAL STATISTICS.—At Westminster Medical School, 6 p.m., Discussion of the Report of the Working Party set up to examine the Assessment of the Need for Clinical Services.

SOCIETY FOR ENDOCRINOLOGY.—At Royal Society of Medicine, 5.15 p.m., special lecture by Dr. G. Pincus: Pathways of Steroid Synthesis in the Animal Organism.

WEST END HOSPITAL FOR NERVOUS DISEASES.—5.30 p.m., neurological demonstration by Dr. T. Rowland Hill.

Wednesday, April 28

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—At Queen Elizabeth Hospital, Birmingham, 8 p.m., clinical meeting.

INSTITUTE OF DENTAL SURGERY.—5.30 p.m., Dr. R. W. G. Wyckoff: Significance of the Electron Microscope in Biology and Medicine.

RENAL ASSOCIATION.—At Ciba Foundation, 4.30 p.m., annual general meeting. Mr. I. H. Griffiths: Renal Arteriography; Dr. R. M. Gaunt: Studies on the Experimental "Eclampsia-like" Syndrome.

ROYAL EYE HOSPITAL.—5.30 p.m., Mr. L. H. Savin: Ophthalmic Neurology (4).

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr T. A. H. Munro: lecture-demonstration in psychiatry.

Thursday, April 29

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., 33rd Silvanus Thompson Memorial Lecture by Professor J. K. Robertson: An Experiment in Medical Education.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: Some Aspects of Sinusitis.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Hammersmith Hospital, 2 p.m., Professor A. Duncan: Histamine and Histaminase in Pregnancy.

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. Gregory Pincus (Massachusetts): Steroids in Ageing.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., debate: That Quackery Plays a Useful Part in Medicine To-day. Proposed by Dr. M. Marcus and Dr. S. H. Chazen; opposed by Dr D. Preiskel and Mr. I. Preiskel.

LONDON UNIVERSITY.—At London School of Hygiene and Tropical Medicine, 5 p.m., special university lecture in hygiene and public health by Dr. E. L. French (Melbourne): Epidemiological Aspects of Murray Valley Encephalitis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor I. P. Todd: Role of Elective Surgery in the Management of Diverticulitis of the Colon.

ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Non-paralytic Squint—The Aim of Modern Methods of Treatment.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Mr. W. M. Dennison: Advances in Surgery of Infancy and Childhood.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., neurology demonstration by Dr. J. H. Paterson.

Friday, April 30

BRITISH INSTITUTE OF RADIOLOGY.—5 p.m., meeting of medical members.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4 p.m., Radiotherapy Section meeting. Professor D. W. Smithers: Rotation Therapy.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical meeting for general practitioners. Mr. W. D. Doey: Indications for Tonsillectomy.

MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES.—7.30 p.m., general meeting. Presidential Address: Personal Reflections regarding the Trichomonas Vaginalis.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Professor A. G. R. Lowdon: Surgical Management of Intestinal Obstruction; 4 p.m., Dr. J. E. Caughey (New Zealand): Hypopituitarism.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Professor J. C. Moir: Obstetric/Gynaecological Conference.

●SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At National Institute for Medical Research, 6.15 p.m., Dr. R. K. Callow: Medical Research and Fine Chemicals.

Saturday, May 1

ASSOCIATION OF CLINICAL BIOCHEMISTS: SOUTHERN REGION.—At Radcliffe Infirmary, Oxford, 2 p.m., meeting. Scientific papers.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 11 a.m., Mr. J. Hamilton: Breech Presentation.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Ball.—On April 9, 1954, at the Central Middlesex Hospital, London, N.W., to Francesca, wife of Dr. Keith Ball, a daughter—Phillida Jane.

Chalmers.—On April 16, 1954, at St. David's Hospital, Cardiff, to Doreen, wife of Dr. T. M. Chalmers, a son.

Gibson.—On April 11, 1954, at The Shiel, Elgin Road, Weybridge, to Graeme (formerly Galbraith) wife of Dr. Eric Gibson, a son.

Helsby.—On April 12, 1954, at Liverpool Maternity Hospital, to Joyce, wife of Raymond Helsby, F.R.C.S., a daughter.

McCarthy.—On April 6, 1954, at Stamford, Lincs, to Agnes (formerly Baker), M.B., B.S., D.A., wife of Cedric McCarthy, a son—James Whyte.

Richardson.—On March 5, 1954, at the Phyllis Memorial Home, Melton, Woodbridge, Suffolk, to Pamela, wife of Dr. J. Derek Richardson, a daughter—Jennifer Anne.

West.—On April 15, 1954, at the Plummer Hospital, Sault-Ste.-Marie, Ontario, Canada, to Kathleen (formerly Stanhope), wife of Michael H. West, M.D., M.R.C.P., of Thessalon, Ontario, a daughter.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Bags Under the Eyes

Q.—*Is there any treatment—surgical or medical—for "bags" under the eyes?*

A.—If the puffiness which occurs in the lower lids with advancing age is due to atony of the muscles of the lower lid allowing the peri-orbital fat to project forwards, fatigue increases the bagginess and this accounts for the variation in degree which is constantly noted.

The treatment is surgical, and consists in removing the herniated fat and tightening up the eyelid by a lateral pull. Very rarely should eyelid skin be removed from the lash edge. The operation is attended by good results, but should be carried out only by a competent plastic surgeon.

The Reticuloses

Q.—*What diseases are included in the "reticuloses"? What criteria are required for diseases to be included in this group?*

A.—Reticulosis is one of those generic terms like neuritis or gastritis which can have a definite connotation but is more often used to mean anything or nothing.

The term was introduced by Letterer[1] in 1924 to describe the histopathology in the organs of a child aged 6 months who died following an acute illness characterized by pyrexia, purpura, aural discharge, and generalized lymph node enlargement with hepato-splenomegaly; there was found to be a widespread proliferation of primitive histiocytes or reticulum cells in the lymph nodes, liver, spleen, bone marrow, and skin. The case is the first clearly described account of the condition known as Letterer–Siwe disease.

Subsequent to this case report, a number of other cases showing generalized proliferations of histiocytes were described, and classifications relating these cases to the leukoses, storage disorders such as Gaucher's disease, and the lymphosarcomata were propounded. Pullinger,[2] in a detailed study of the histology of Hodgkin's disease, suggested that a group of diseases of the reticular tissue exists in which differentiation is possible into one or several of the possible cell progeny, and following this Ross[3] and Robb-Smith[4] put forward detailed classifications based on anatomico-histological divisions which included both definite disease entities such as Hodgkin's disease, the leukaemias, and storage disorders, as well as reactive change of lympho-reticular tissue; there have been numerous modifications of these classifications such as those of Symmers[5] and Israels.[6] On the Continent there has of recent years been a tendency, as shown by van der Meer and Zeldenrast[7] or Cazal,[8] to restrict the term reticulosis to those conditions in which there is a proliferation of histiocytes or their precursors rather than to use it in the broad sense of English writers. In America the term reticulosis is little used, as they have adopted an all-embracing term "lymphoma" (Custer and Bernhard[9]) which includes the progressive hyperplasias and the sarcomata, whereas in England and on the Continent there is a clear distinction made between these two types of tissue reaction, although in certain instances the progressive hyperplasia may alter so as to become sarcomatous.

If we follow English usage of the term "reticulosis" we can define it as a generic histological term to describe all the hyperplasias of the reticular tissue. These can be divided into two large groups, the reactive or reversible

hyperplasias or the progressive or irreversible hyperplasias; usually the term "reticulosis" is restricted to the latter group. The reactive or reversible hyperplasias of reticular tissue include a large range of infective disorders characterized by hyperplastic or granulomatous proliferations of reticular tissue, such as typhoid fever, tuberculosis, perhaps sarcoidosis, histoplasmosis, malaria, leishmaniasis, and many more; it also includes the reactive conditions in which there is no known aetiological cause, such as sinus catarrh, reactive hyperplasia, and perhaps the storage disorders, because, although these are not usually reversible, they may be on occasions and there is some knowledge of the proximate biochemical lesion. The progressive hyperplasias include the leukoses (lymphoid, myeloid, and monocytic, whether aleukaemic or leukaemic), di Guglielmo's disease and myelomatosis, lymphoid follicular reticulosis (follicular lymphoblastoma), lymphoreticular medullary reticulosis (the majority of cases of Hodgkin's paragranuloma (Jackson and Parker[10]) and benign Hodgkin's disease (Harrison[11]), Hodgkin's disease (lymphadenoma verum), mycosis fungoides, myelosclerosis (osteosclerotic myelopathy), histiocytic medullary reticulosis, and reticulum-celled medullary reticulosis (Letterer–Siwe syndrome, eosinophil granuloma, Hand–Schüller–Christian syndrome, reticuloendothelial granuloma, histiocytosis X (Lichtenstein[12])).

It should be realized that the term "reticulosis" is a generic morphological term and not a clinical term, unless qualified by its specific histological characters. To say that a patient has "a touch of reticulosis" is probably less informative than to say that a patient has enlarged lymph nodes, though, as Arnold of Villanova pointed out a long time ago in respect of another term, it might sound more impressive.

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Deodorants in General Practice

Q.—*I would be grateful for your suggestion for a good deodorant which can be used by our district nurses in private houses when doing very offensive dressings.*

A.—No deodorant is known which gives satisfactory results under the conditions stated. The problem presents two phases for consideration: (1) Is it possible to deal quickly with a relatively large volume of foul gas suddenly released into the air of the bedroom when dressings are removed? (2) Is there a method for dealing with the slow trickle of foul gas which is continuously escaping from the affected tissues?

There is much to be said theoretically for spraying the room with solutions of substances which react chemically with the offensive gas and thus change it to an odourless compound. In practice there are difficulties: the deodorizing solution must be non-toxic to man and animals, and it must not damage the furnishings by staining, bleaching, corrosion, etc. It has been claimed that certain chlorophyll derivatives act as deodorants in this way, but the claim has been vigorously disputed.

The cleansing and deodorizing of offensive wounds and skin surfaces can be achieved by the local application of active carbon (charcoal), but only those preparations should be used which are guaranteed by the manufacturers to be potent adsorbents. There may also be a place for an inexpensive air-filtering apparatus consisting of a box fitted with a fan which sucks the air through a deodorizing screen containing active carbon. The method is most effective against gases which have a high molecular weight—such as the mercaptans—and *per contra* least effective when the molecular weight of the gas is low, for example, with sulphuretted hydrogen and ammonia.

A charcoal blanket has been devised for use in cases where there is intractable foul discharge—for example, in inoperable cancer of the uterus or rectum. The principle consists in screening the patient from the neck to the feet with material which contains particles of active carbon. This has been shown to be effective under controlled experimental conditions and in clinical practice. Nevertheless it fails if the nurse or the patient omit to carry out the simple instructions; and of course it ceases to act as a filter when it is removed with the other bedclothes preparatory to dressing the wound.

Patients with offensive discharges from colostomies can also be treated with active carbon in small doses by mouth, say half a teaspoonful four times daily. The powdered carbon is made more manageable if it is moistened with water to make a paste. The same method can be used for other patients who pass offensive stools. It must be remembered, however, that prolonged oral medication with active carbon may possibly interfere with nutrition by adsorption of enzymes and other essential substances in the alimentary canal.

Luminous Paint

Q.—*How much radiation is given off by luminous paint? Have any examples been reported of radiation damage to users (as opposed to manufacturers) of articles coated with luminous paint?*

A.—Radioactive luminous compound usually contains radium, though occasionally a mixture of radium and mesothorium is employed. The amount of radium used per gramme of compound is of the order of 70 μC for instrument dials (for example, for aircraft), of 38 μC for watches, and of 12 μC for alarm clocks. As will be appreciated, only minute quantities of compound are used for luminizing watches and clocks. No case has been reported of radiation damage to users of luminized objects.

3-D in a Medical Journal.—The editorial manager of *Medicine Illustrated* has written to point out that last November's issue of that journal included a supplement with stereoscopic illustrations. This controverts the claim for priority made by the editor of *Anaesthesia* (see *British Medical Journal*, April 10, p. 886).

"Any Questions?" Book.—The second book of selected "Any Questions?" is available, price 7s. 6d. (postage 6d.). Copies may be obtained either direct from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1, or from booksellers.

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